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CALCIUM AND PHOSPHORUS AND

SMITH,[1] describing the medical treatment of 314 cases of bronchial asthma writes: "When a patient was found to be sensitive, the need for general treatment was explained in detail. The general health of the subject was considered, and he was usually put on a regimen of proper rest and dietary measures, with cod liver oil and calcium lactate in moderate doses."

Novak and Hollander[2] in their study of the serum calcium of 87 patients with hay fever, hyperesthetic rhinitis and the asthmas state that the ionic calcium content of the blood serum is invariably low in hyperesthetic rhinitis and that there are also certain cases of hay fever and asthma which show a low calcium content. Calcium compounds and thyroid extract afforded temporary relief but when combined with vitamin D therapy in the form of ultra-violet irradiation it appeared to have a permanent influence on all of the rhinitis cases and upon approximately 50 per cent of those in the latter two groups.

Sterling[3] writes: "Calcium is beneficial in most hypersensitive cases whether they show a low blood calcium or not. Both calcium and phosphorus help to control the hyperexcitability of the nervous system. . . . While we cannot draw positive conclusions from a study of the above cases, calcium and phosphorus are found of great benefit in the treatment of allergic diseases. This mineral deficiency in asthmatics, hay fever, and allied diseases, whether sensitivity can be proved or not, may be the missing link which makes the allergic differ from the normal. The addition of calcium, phosphorus, and other minerals, for instance, iron, sodium and potassium salts, are possibly responsible for the favorable results in this series of cases."

Burgess[4] is of the belief that cases of urticaria, especially those showing marked dermographism, and eczema in the vast majority of instances present a marked diminution of precipitable serum calcium. He reports that cases of urticaria and eczema were considerably improved by measures to raise the serum calcium.

Kitsuta[5] reports that in his own case he used cod liver oil and yeast for the treatment of hay fever, with beneficial results. He states: "In administering cod liver oil for the cure of hay fever already developed, I think it advisable to take about 4 teaspoonfuls three times daily. . . ."

Jones[6] found 60 per cent of his cases of exudative diathesis improved with calcium medication and parathyroid extract.

Mollison[7] states that 37 per cent of 40 cases of vasomotor rhinitis were cured and 27 per cent improved by calcium compounds and measures to increase calcium absorption.

Von Gordon[8] believes that hay fever and asthma are neuroses based upon a functional disturbance of the vegetative nervous system leading to a sympathetic hypotonia with or without vagotonia, and to a labile equilibrium of the vagus sympathetic nerves which react pathologically to normally inadequate stimuli. He contends also that a decrease in the blood calcium is one of the most important causes of this lability.

Colomb[9] states that from a therapeutic standpoint calcium is valuable for conditions associated with anaphylactic phenomena. He adds, its absorption is regulated by vitamin D.

Hutton[10] states that disturbances of calcium metabolism are likely to be present in urticaria and eczema.

Pottenger[11] thinks that calcium is definitely identified with sympathetic action. He was successful in completely relieving the paroxysms of asthma by means of calcium therapy.

Klare[12] believes that there is a relationship between the exudative diathesis of childhood and calcium deficiency. He therefore finds calcium therapy indicated in recurrent catarrh, bronchial asthma, hay fever, adenopathies and increased susceptibility to acute infections. He believes that calcium has a specific action in decreasing the hyperirritability of the autonomic nervous system.

Downing and Blumenfeld[13] report several cases of acute and chronic urticaria in which calcium therapy was effective.

Schmidt[14] found ultra-violet light of value in his own case and attributed the result partly to the antispasmodic effect of the treatment.

Ochsenius[15] points out that calcium (*Cont'd*)

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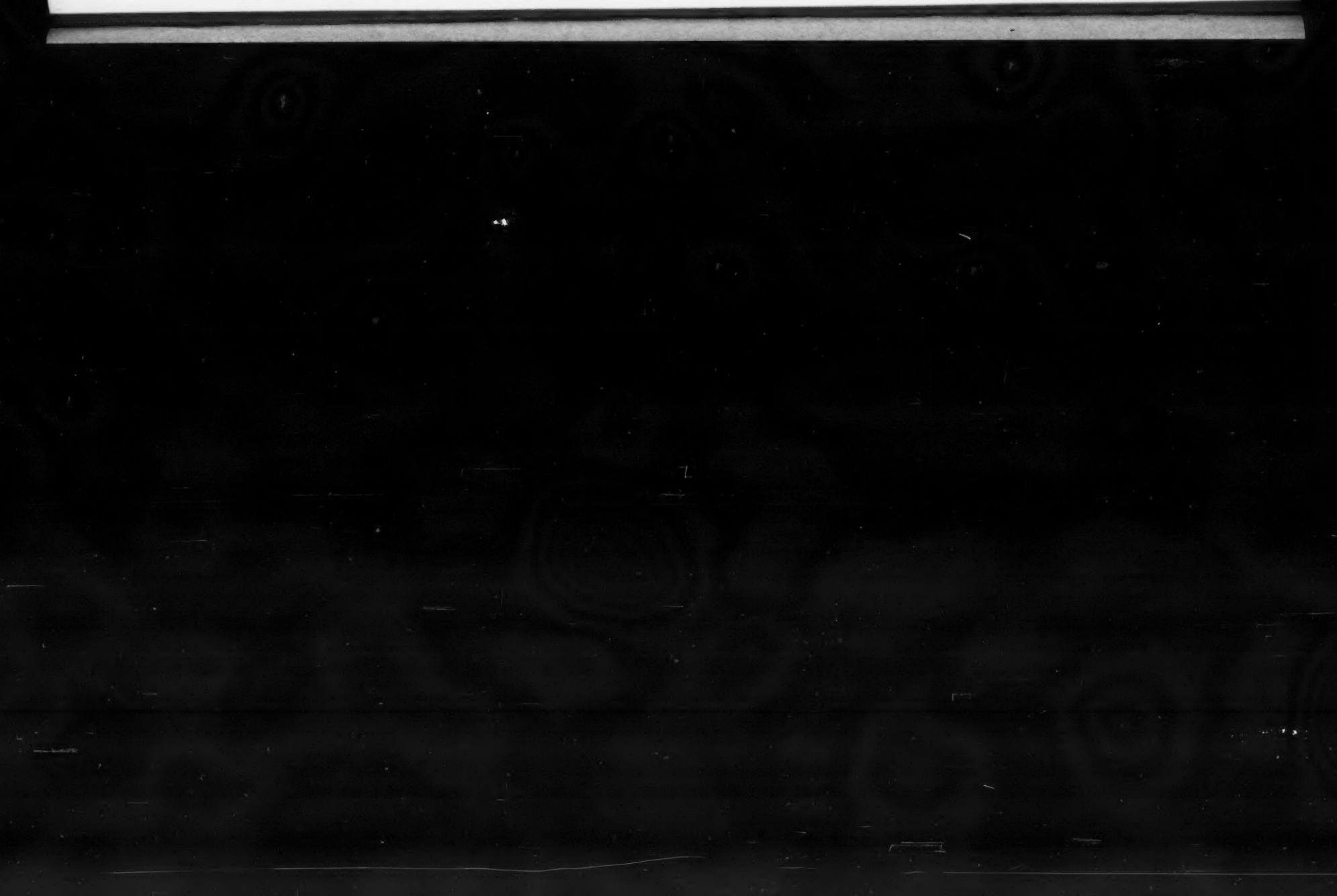

The Journal of Allergy

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Original Articles

THE PREPARATION AND STANDARDIZATION OF POLLEN EXTRACTS FOR THE TREATMENT OF HAY FEVER*†

ROBERT A. COOKE, M.D., AND ARTHUR STULL, PH.D.
NEW YORK, N. Y.

THE necessity for uniformity or standardization of the extracts of pollen used in the diagnosis and treatment of hay fever was apparent to the earliest workers in the field of allergy, and attempts were made to standardize extracts. Noon[1] used as a unit that quantity of pollen toxin extracted from one-millionth gram of pollen. Cooke[2] standardized saline extracts of pollen by the total nitrogen content. Clock[3] recommended a standardization method depending upon the complement fixation capacity of pollen extracts against antipollen serum.

Noon's unit is used by some and modified by others. Both the methods of Noon and of Cooke are subject to the errors that will be pointed out in this paper. Armstrong and Harrison[4] showed that the complement-fixation capacity of ragweed pollen was not related to the essential desensitizing factor of the pollen extract. No accurate method has heretofore been presented.

Investigation by the writers[5, 6, 7, 8] with Chobot and with Barnard has shown that in giant (*Ambrosia trifida*) and low ragweed (*Ambrosia artemesiaefolia*), timothy (*Phleum pratense*) and certain other grass pollens, an albumin fraction of the pollen, which gave characteristic tests and analysis for protein, was the allergically active factor producing hay fever. This work opened the way for the standardization of pollen extracts on a protein basis. Such a method would give a unit directly related to the content of active material. Saline extracts of these pollens contained traces of inactive protein material (probably globulin), but the amounts were so small in proportion to the albumin that they did not interfere with the method of standardization presented here.

Evidence of the inaccuracy of present methods of standardization was

*From the Department of Medicine of the New York Hospital and Cornell University Medical College and the Department of Allergy of Roosevelt Hospital.

†Read before the Society for the Study of Asthma and Allied Conditions, December 10, 1932.

shown by the fact that different lots of ragweed, timothy, and certain grass and tree pollens when extracted under identical conditions from the same weight of pollen varied in the amount of active substance expressed as protein nitrogen.

TABLE I

ALKALINE SALINE FLUID EXTRACTS FROM 3 GM. DEFATTED POLLEN PER 100 C.C. EXTRACTED AND ANALYZED FEBRUARY, 1932

POLLEN	TIMOTHY			HICKORY (HICKORIA GLABRA)		RAGWEED	
Season collected	1921	1928	1931	1927	1931	1923	1931
Total N. mg. per c.c.	.21	.14	.37	.39	.41	.37	.46
Protein N. mg. per c.c.	.05	.06	.20	.15	.09	.09	.15
Protein N. as per cent of total N.	24	43	54	38	22	24	32

Pollen extracts differing in age did not contain the same proportion of protein nitrogen to the total nitrogen.

TABLE II

ROUTINE POLLEN EXTRACTS ANALYZED FEBRUARY, 1932

POLLEN	TIMOTHY		RAGWEED	
Year extracted	1931	1932	1931	1932
Total N. mg. per c.c.	.38	.40	.63	.62
Protein N. mg. per c.c.	.08	.20	.14	.16
Protein N. as per cent of total N.	21	50	22	26

Supposedly comparable extracts, therefore, when standardized on a total nitrogen (Cooke) or weight (Noon) basis varied in the amount of protein nitrogen, and clinical experience has shown that they vary greatly in activity. Tables I and II show that in certain extracts on a weight per volume basis the protein variation was as great as 75 per cent, and on a total nitrogen basis it ran as high as 50 per cent. When such extracts were diluted on a protein nitrogen basis, they compared favorably in activity. Furthermore, on this protein basis, one-year-old and new extracts have been given interchangeably in therapeutic doses without constitutional reactions.

The Preparation of Pollen Extracts.—The dry pollen was completely defatted under anhydrous conditions in a Soxhlet with petroleum ether or c. p. anhydrous ethyl ether and kept dry until used. This ether soluble material interfered with the extraction of the protein, and Bengtsson[9] has shown that the ether soluble material from ragweed produced on patch test a severe dermatitis on certain cases not necessarily subject to ragweed hay fever. Subsequent work[10] has confirmed this, and others[7] have shown

that the ether soluble material of timothy and other grass pollens may also produce dermatitis. The complete removal of this ether soluble material was indicated in order to avoid the danger of producing dermatitis in extremely susceptible individuals and to facilitate the extraction of active material.

Coca[11] modified Cooke's procedure by the addition of sodium bicarbonate to the sodium chloride solution, and later[12] recommended the saturation of the fluid with carbon dioxide. We have found that carbon dioxide was not necessary when a pure bicarbonate was used.

The alkaline saline fluid for pollen extraction was composed of 0.5 per cent sodium chloride, 0.275 per cent sodium bicarbonate c. p. and 0.4 per cent phenol in distilled water. Depending upon the strength required, from 3 gm. to 12 gm. of defatted pollen were extracted in 100 c.c. of alkaline saline fluid at about 7° C., for not more than eighteen hours. A few hours' extraction removed as much nitrogen and active material as long periods. The use of more pollen than 12 gm. per 100 c.c. may result in less complete extraction, and in very concentrated extracts precipitation resulted.

After the extract had been filtered from the pollen through paper on a Büchner funnel, it was sterilized by filtration through a Seitz or Berkefeld filter. It was tested for sterility according to government requirements. Protein nitrogen was then determined as next described. This stock extract was diluted for test and injection with sterile buffered saline made according to Evans.[13] Phenol to 0.4 per cent was added.

Standardization.—Phosphotungstic acid was used to precipitate the protein in estimating the protein nitrogen in the extracts. Phosphotungstic acid precipitated all the nitrogen and activity from solutions of the purified protein albumin of ragweed and timothy pollen. Also the whole extracts of timothy and ragweed pollen after dialysis in a hardened membrane against distilled water contained nondializable active protein nitrogen of the same magnitude as determined by phosphotungstic acid precipitation. This method gave accurate results. A direct turbidimetric method using sulphosalicylic acid was not sufficiently accurate.

The total nitrogen was determined in duplicate on 5 to 10 c.c. portions of the concentrated pollen extract by the Kjeldahl method. The nonprotein nitrogen was determined in duplicate on 5 to 10 c.c. portions of the concentrated extract by the addition to each of 2.5 c.c. concentrated hydrochloric acid and about 1 c.c. of 10 per cent phosphotungstic acid in 10 per cent hydrochloric acid solution. Phosphotungstic acid was used in excess to insure complete precipitation of protein. The solutions were shaken, allowed to stand for two hours, when the precipitate was filtered off and washed free of nonprotein nitrogen. A Kjeldahl determination on the filtrate and washings gave the nonprotein nitrogen. The difference between the total and nonprotein nitrogen gave the protein nitrogen. The

method gave checking results within 0.02 mg. nitrogen per cubic centimeter and was accurate in solutions containing 0.1 mg. protein nitrogen per cubic centimeter. In general, 3 to 4 gm. of pollen per 100 c.c. of alkaline saline fluid gave extracts containing sufficient protein nitrogen for the analysis. This analysis for protein nitrogen can be applied to extracts containing glycerin.

Stock extracts and dilutions of extracts after analysis must not be subsequently filtered, or, if filtered, they must be reanalyzed, as protein was removed by the filter. A dilution of timothy pollen (0.05 mg. protein nitrogen per cubic centimeter) was filtered through a Seitz filter four times. Analysis then showed that the nonprotein nitrogen was the same as in the original dilution, but the protein nitrogen had been removed. By clinical test it was inactive.

The concentrated stock extract and dilutions, preserved at a temperature not higher than 10° C., deteriorated slowly. Ragweed extract deteriorated more slowly than timothy. Analysis has shown that a timothy extract originally containing 0.2 mg. protein nitrogen per cubic centimeter contained 0.14 mg. protein nitrogen per cubic centimeter (a loss of approximately 33 per cent), when analyzed eight months later. Extracts that were one year old when restandardized on a protein nitrogen basis were comparable in activity with fresh extracts similarly standardized, whereas a sixteen-year-old extract, while active, was not comparable with a new extract even when diluted on a protein nitrogen basis. Protein in solution seemed to undergo some alteration modifying its allergic activity, and therefore it is necessary for extracts to be marked with an expiration date of one year following date of preparation comparable with other biologic products.

Standard Unit.—With the establishment of the protein nature of the active substance in pollen producing hay fever, it was evident that the nitrogen which was a constant and easily determinable element in protein would serve as the basis of standardization. Through long experience with pollen extracts, it has been empirically established that a protein nitrogen fraction of 0.00001 mg. was practically the smallest dose that would be required for the most sensitive patient. Therefore, such a fraction may be suggested as one unit. One hundred units would be 0.001 mg. protein nitrogen and 0.1 mg. represents 10,000 units. The scale of dosage would lie well between 1 and 100,000 units. The concentration of extracts would be expressed in units per cubic centimeter.

DISCUSSION

In view of the fact that there was a deterioration of active substance in extracts carefully preserved at 7° C., it might be inferred that it was not yet time for any attempt at a standardization of such unstable extracts. In answer to this it can be said:

(1) The loss of active substance was not extreme except in the case of the timothy and possibly other grass pollen extracts.

(2) This loss of active substance can be compensated for by an increased dosage, since the remaining protein is as active as that in fresh extracts.

(3) The principle of protein standardization was correct and will still be applicable if and when nondeteriorating extracts are produced.

A knowledge of the potency of extracts is advantageous whether treatment is preseasonal, coseasonal or perennial and particularly so in the latter instance, since the change from the old extract to the new may be made with accuracy without loss of time and with less danger of constitutional reactions.

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STUDIES ON POLLEN AND POLLEN EXTRACTS*

IX. A New Extracting Solution

Leon Unger, M.D., and Marjorie B. Moore, Ph.D.
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OF THE various solutions used at the present time for extraction of pollens, there is none which gives an extract perfectly satisfactory in all respects. Extracts prepared with saline solutions with or without the addition of ethyl alcohol are relatively unstable. When the extracting menstruum contains a high percentage of glycerin, a product is obtained which is quite stable but has the disadvantage that its injection causes considerable pain. The effect of the glycerin is such that these extracts cannot be used for intracutaneous testing. Moreover, the high vicosity of extracts containing the usual proportion of glycerin makes it quite difficult to force them through small needles.

We have studied various kinds of aqueous solutions for extraction of pollens with the purpose of finding one which would give an extract not only of good stability, but so acceptable to the tissues that it might be used intracutaneously as well as subcutaneously without nonspecific irritation.

All the work which has been done on active fractions from the common hay fever pollens indicates that aqueous solvents, even distilled water, are capable of extracting practically all the allergenic substance. The proponents of the idea that the allergen is of protein nature have found that the active protein is extracted by water. All investigators seem to agree that the glutelin fraction is probably inactive or of very minor importance. Some protein of globule nature is extracted by distilled water because of the salts present in the pollen itself.[1] However, the most active protein fraction appears to be albuminous in nature. The work of Stull, Cooke and Chobot[2] indicates that this may constitute the only allergen in a number of different pollens. Likewise, the specific polysaccharide first isolated by Black[3] from ragweed pollen is extremely soluble in water.

PREPARATION OF EXTRACTS

Assuming that all the active material is extractable by distilled water, there remains the problem of adding some substance which will prevent deterioration of the extract. Dextrose has been found to be very effective for this purpose. In isotonic solution, 5 per cent, it gives a pollen extract which is relatively painless upon injection and may be used either subcutaneously or intracutaneously without irritation.

As the dextrose does not possess the bacteriostatic properties of glyc-

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erin, a small percentage of an antiseptic agent is added to lessen the possibility of bacterial contamination. The solution which we have used consists of 5 per cent dextrose and 0.1 per cent cresol in distilled water. The whole pollen is then extracted with this solution in the usual manner, filtered and passed through a Berkefeld filter for sterility. A precipitate which forms in the extracts upon standing consists of a glucoside of whose origin we are not yet certain, but which has been found inactive. Its formation or precipitation seems to be hindered by glycerin. If a crystal-clear extract is desired, the solution may again be filtered without loss of potency.

TESTS ON RABBITS

Before proceeding to test such extracts upon patients or to use them for treatment, experiments were conducted upon ragweed sensitized rabbits to show their potency and stability. The method of animal testing used was the trypan blue skin test procedure first described by Ramsdell[4] and applied quantitatively to pollen extracts by Cromwell and Moore.[5] The comparison is carried out with serial dilutions of the extracts to be tested, the technic being quite similar to that used in quantitative intracutaneous testing upon hay fever patients.

The first tests upon rabbits compared the potency of ragweed pollen extracts prepared by the use of distilled water, Coca's solution, and glycerosaline solution prepared from equal volume of Coca's solution and glycerol. No significant difference could be shown in the potency of such extracts prepared from the same sample of pollen. Later in the course of the work, in order more definitely to establish the extracting efficiency of the dextrose solution, an extract of giant and short ragweed and burweed marsh elder pollens prepared with the dextrose solution, was compared with a similar extract of the same pollens in glycerosaline solution. Using ragweed sensitized rabbits, quantitative skin tests showed no detectable

TABLE I

COMPARISON OF FRESHLY PREPARED GLYCEROSALINE AND DEXTROSE SOLUTION EXTRACTS OF POLLEN. POLLEN UNITS REPRESENTED PER C.C. IN MOST DILUTE SOLUTION SHOWING POSITIVE REACTION.

RABBIT NO.	GLYCEROSALINE EXT.	DEXTROSE EXT.
550	100	1*
537	10	1*
535	100	100
575	1000	1000
562	1*	1*
11	100	†
448	10	1*

*Highest dilution tested; gave distinct reaction.
†Solution containing 1000 units per c.c. failed to react.

difference in potency of the two extracts. The same extracts were used for comparison upon patients. It may be noted that rabbits, like human subjects, vary in their reactivity and it is necessary to consider the series as a whole in drawing conclusions.

In the first experiment, to study the efficiency of various solutions, they were used to dilute a 3:100 glycerosaline extract of giant ragweed pollen to 1:5000. These dilutions were then incubated for five months (37° C.), then left at room temperature for six months before testing. In this case, only qualitative skin tests were carried out upon sensitized rabbits. The 1:5000 solutions were again diluted to make 1:10,000, and tests were made with these. A 1:1000 fresh pollen extract was used to show sensitivity of the animals. Thus it was observed that a diluting solution containing 5 per cent dextrose with 0.1 per cent cresol had preserved the potency of the extract so that qualitatively it gave as pronounced reactions as the fresh pollen extract.

As the dextrose solution proved so effective in preserving potency when used as a diluent, a further experiment was carried out to study the stability of dextrose solution extracts containing no glycerol. Ragweed pollen (short and giant) extracts (3:100) were prepared in glycerosaline solution and in an aqueous solution of 5 per cent dextrose with 0.1 per cent cresol. After filtration for sterility, samples of these extracts were placed in the incubator. The two extracts were then compared by quantitative skin tests upon sensitive patients at intervals up to one year. After a year's incubation, comparative skin tests were made upon rabbits sensitized to mixed short and giant ragweed pollen. These tests showed that the potency of the two types of extracts had remained practically equal and that both retained a high degree of activity even under such adverse conditions.

TABLE II

COMPARISON OF POLLEN EXTRACTS IN GLYCEROSALINE AND DEXTROSE SOLUTIONS AFTER INCUBATION FOR ONE YEAR. POLLEN UNITS REPRESENTED PER C.C. IN MOST DILUTE SOLUTION SHOWING POSITIVE REACTION.

RABBIT NO.	GLYCEROSALINE EXT.	DEXTROSE EXT.
11	0.1*	0.1*
537	0.1*	0.1*
448	†	1000
562	1	1

*Highest dilution tested; gave distinct reaction.
†Solution containing 1000 units per c.c. failed to react.

COMPARATIVE TESTS ON HAY FEVER CASES

The next step was to compare skin test reactions in the human being. Ragweed sensitive individuals were chosen at random, and comparative tests were made with freshly prepared extracts and at intervals of two,

four and a half, and nine months, and one year, the time from the preparation and beginning of incubation of the two solutions. Dilutions from 1:10,000 to 1:100,000,000 were made in most cases. In four patients 1:1,000 dilution was also used. Tests were made on the forearms, with comparative dilutions of both the glycerosaline and dextrose solutions; the weakest dilutions of each were injected intracutaneously (0.02 c.c.) toward the bend of the elbows; the strongest toward the wrists. Five per cent dextrose solution containing 0.1 per cent cresol was used as the control.

A study of Table III reveals that in the 21 comparative tests the glycerosaline extracts were a little stronger in four cases; in three, the dextrose solutions gave somewhat larger reactions. In the other 14 the tests were approximately equal on the two arms. It must be emphasized that there was very little difference shown between the two extracts. From the standpoint of comparative skin tests, then, the two are about equal.

TABLE III

PERIOD OF INCUBATION	PATIENT	RESULTS TESTS
Freshly prepared	1 O. G.	Equal
	2 A. L.	Equal
Two months	3 M. V.	Equal
	4 E. F.	Equal
Four and one-half months	5 M. V.	Dextrose slightly stronger
	6 A. N.	Equal
	7 A. D.	Equal
Nine months	8 B. Z.	Glycerosaline stronger
	9 O. G.	Equal
	10 R. S.	Equal
	11 A. D.	Glycerosaline stronger
	12 M. A.	Equal
	13 D. T.	Dextrose slightly stronger
	14 H. B.	Glycerosaline slightly stronger
	15 M. V.	Dextrose slightly stronger
	16 M. D.	Equal
	17 P. D.	Equal
One year	18 L. B.	Equal
	19 E. M.	Glycerosaline stronger
	20 D. P.	Equal
	21 R. G.	Equal

CLINICAL RESULTS

The glycerosaline extracts of pollen have, of course, been in use for many years, so that a *good* evaluation of their efficiency is available. The new dextrose solution, on the other hand, has been tried by only a few men and not very extensively, as yet, by any one; so that an accurate clinical test is not available at this time. However, the opinions of some clinicians may be of interest.

Dextrose extracts of mixed ragweed pollen were mailed out in early 1932 to fourteen men who specialize in allergy in various cities of the United States. They were asked to try these out on hay fever cases and to compare their efficiency with that of the usual glycerosaline solution. The following is a brief summary of their replies:

A. is very favorably impressed with the new dextrose solution. He states that it is just as potent as the glycerosaline extracts, and much less painful. He has tried it in seventy-five cases.

B. likes the new solution much better. He has also found both extracts equal as measured by comparative skin tests, and prefers the dextrose solution because it is painless and can be used for intradermal testing.

C. also prefers the dextrose extracts for similar reasons; he further says, "I am convinced that many become sensitized to glycerin which may be the cause of urticaria and other types of dermatitis."

D. did not make comparative skin tests but had favorable results in the three cases tried.

E. found that the glycerosaline solution gave larger skin tests, but felt that the results, clinically, are about equal.

F. feels that further clinical trial is necessary, but is favorably inclined.

On the other hand, there were some unfavorable comments.

G. objected to the dextrose solution because on settling a brownish precipitate appeared. This is due to a harmless glucoside and has now been eradicated. Clinically one case treated by G. was a failure.

H. found the dextrose solution not so potent on comparative skin tests and did not treat any patients with it.

J. found the trial dextrose extract to be less potent on skin tests and did not try any clinically.

The other men to whom extracts were mailed have not tried the dextrose solution sufficiently, or at all.

One of us (L. U.) has tried out the dextrose extracts on forty-one private patients. However, the new extract was used in these only after June, 1932; the patients were changed over from the glycerosaline extracts. In these cases there was no discomfort caused by the transfer; all the patients seemed greatly pleased because of the marked lessening of pain on injections; and, clinically, the results were about the same as in those who received the glycerosaline extracts throughout. Incidentally, about the same percentage of local and systemic reactions occurred with each extract.

The new solution seems particularly gratifying because of its lack of pain, and this feature is especially useful in treating children and the "nervous" type of adults. In addition, its use enables one to give larger injections.

From the clinical point of view, then, this is only a preliminary report. For the next season we intend to treat comparative groups of hay fever

cases with the two solutions and hope to report again next year. In addition, we anticipate that the painlessness of the dextrose solutions will enable us to reach much higher dosages than heretofore, and we hope that this will bring with it better clinical results.

CONCLUSIONS

1. It has been shown that the extract of mixed ragweed pollens in cresolized 5 per cent dextrose solution is about as stable as is the glycerosaline extract; that it is much less painful; and that it is better in that it can be more easily drawn through fine needles and can be used for intracutaneous tests as well as for treatment.

2. Comparative skin tests on rabbits and in the human on hay fever patients have demonstrated no essential difference between the two.

3. Clinical results are as yet uncertain, but are at least sufficiently favorable to warrant further studies.

The authors wish to express their appreciation to Mr. Edgar B. Carter, Director of Biologic Laboratories, Abbott Laboratories, for his advice and helpful suggestions and to Miss Constance Seeber for the technical assistance in the animal work.

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NOTES ON THE TREATMENT OF HAY FEVER*

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IN A recent study of hay fever[1] we have observed the changes that occur in the dermal tests following specific pollen therapy. In the 44 patients studied, the skin tests became extinct in 9 per cent of the cases, decidedly diminished in 81 per cent and remained unchanged in another 9 per cent at the end of the treatment season. Further analysis of this study indicated that the clinical end-results from treatment closely corresponded to the changes in the skin tests, except in a few instances where factors other than pollen sensitivity were at play.

In the present communication we are concerned with the evaluation of the influence of the number of doses, the quantity of pollen extract used and the incidence of other sensitization on the end-results of therapy in this group. The frequency of treatment and the extent of the local reactions are also worthy of comment.

In this group of 44 patients, 34 suffered from ragweed hay fever with symptoms in August and September, 2 had grass hay fever with symptoms in June and July, while 8 had combined ragweed and grass hay fever.

As a result of pollen therapy complete relief from seasonal hay fever was obtained by 5 ragweed and 1 grass pollen case; marked relief by 27 ragweed, 1 grass and 5 combined ragweed and grass cases, slight relief was experienced by 1 ragweed and 2 combined ragweed and grass cases, while failure at relief was noted in 1 ragweed case.

In Table I the end-results of treatment are plotted against the number of doses, the size of the final dose and the amount of pollen extract administered in each case. It will be noted from this chart that the five ragweed cases with complete relief received various numbers of doses ranging from thirteen to twenty-five, while the 27 ragweed cases with "marked relief" show a range of variation from fourteen to fifty-one doses. Similar differences in dosage are noted in the 8 combined grass and ragweed cases, as well as in the 2 pure grass cases.

We further observe from this chart that the size of the final dose varies considerably in different patients in this group, that it is unrelated to the total amount of pollen used, and that it bears no constant parallelism to the number of treatments administered to the individual patient. For example, a final dose of 1.00 c.c. of 1:500 pollen dilution was reached in 11 ragweed cases. The respective number of doses and total amount of pollen administered to each one of these are shown in Table II.

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*From the Anaphylactic Clinic of the Beth Israel Hospital, Brookline, and the Anaphylactic Clinic of the Massachusetts General Hospital, Boston.

TABLE I

THE END-RESULTS OF TREATMENT ARE PLOTTED AGAINST THE NUMBER OF DOSES, SIZE OF THE FINAL DOSE AND THE TOTAL AMOUNT OF POLLEN EXTRACT ADMINISTERED IN EACH CASE

Ragweed Cases

CASE NO.	TOTAL DOSES	FINAL DOSE + TOTAL AMOUNT OF POLLEN IN 1:500 DILUTION		RELIEF
1	13	0.60 c.c.	2.50 c.c.	Complete
2	18	1.00 c.c.	9.60 c.c.	Complete
3	20	0.20 c.c.	3.15 c.c.	Complete
4	23	2.00 c.c.	15.35 c.c.	Complete
5	25	0.25 c.c.	2.75 c.c.	Complete
6	14	1.00 c.c.	1.20 c.c.	Marked
7	16	0.75 c.c.	5.90 c.c.	Marked
8	18	0.60 c.c.	6.25 c.c.	Marked
9	18	0.60 c.c.	4.85 c.c.	Marked
10	18	1.50 c.c.	12.95 c.c.	Marked
11	19	0.50 c.c.	4.80 c.c.	Marked
12	19	1.00 c.c.	7.90 c.c.	Marked
13	19	1.50 c.c.	11.65 c.c.	Marked
14	19	0.35 c.c.	3.05 c.c.	Marked
15	20	0.75 c.c.	10.75 c.c.	Marked
16	20	1.00 c.c.	9.75 c.c.	Marked
17	20	1.00 c.c.	10.80 c.c.	Marked
18	20	0.05 c.c.	0.55 c.c.	Marked
19	20	0.50 c.c.	5.60 c.c.	Marked
20	21	0.90 c.c.	10.30 c.c.	Marked
21	21	0.75 c.c.	7.50 c.c.	Marked
22	21	1.00 c.c.	8.92 c.c.	Marked
23	22	1.00 c.c.	8.50 c.c.	Marked
24	22	0.60 c.c.	8.90 c.c.	Marked
25	22	1.00 c.c.	12.35 c.c.	Marked
26	22	0.25 c.c.	4.85 c.c.	Marked
27	24	1.00 c.c.	14.40 c.c.	Marked
28	24	1.00 c.c.	11.50 c.c.	Marked
29	24	1.00 c.c.	7.85 c.c.	Marked
30	25	0.70 c.c.	6.70 c.c.	Marked
31	33	0.60 c.c.	5.85 c.c.	Marked
32	51	0.75 c.c.	19.25 c.c.	Marked
33	20	1.25 c.c.	9.85 c.c.	Slight
34	22	1.50 c.c.	17.35 c.c.	No relief

Combined Ragweed and Grass Cases

CASE NO.	TOTAL DOSES		FINAL DOSE + TOTAL AMOUNT OF POLLEN IN 1:500 DILUTION				RELIEF	
	G	R	G	R	G	R	G	R
1	16	19	0.25 c.c.	0.50 c.c.	1.50 c.c.	3.85 c.c.	Marked	Marked
2	17	18	1.75 c.c.	1.25 c.c.	16.95 c.c.	11.05 c.c.	Marked	Marked
3	18	15	1.00 c.c.	0.75 c.c.	17.95 c.c.	6.00 c.c.	Marked	Marked
4	21	20	0.50 c.c.	1.50 c.c.	17.25 c.c.	16.85 c.c.	Marked	Marked
5	25	20	0.50 c.c.	0.60 c.c.	7.90 c.c.	5.50 c.c.	Marked	Marked
6	15	14	0.50 c.c.	0.50 c.c.	5.50 c.c.	4.90 c.c.	Slight	Marked
7	11	20	1.50 c.c.	1.00 c.c.	13.20 c.c.	6.65 c.c.	Slight	Slight
8	32	21	0.20 c.c.	0.05 c.c.	4.75 c.c.	0.60 c.c.	Slight	Slight

TABLE I (CONTINUED)

Grass Cases

CASE NO.	TOTAL DOSES	FINAL DOSE + TOTAL AMOUNT OF POLLEN IN 1:500 DILUTION		RELIEF
1	23	2.00 c.c.	24.80 c.c.	Complete
2	27	1.00 c.c.	12.30 c.c.	Marked

TABLE II

CASE NO.	TOTAL DOSES	FINAL DOSE	TOTAL AMOUNT OF POLLEN IN 1:500 DILUTION
6	14	1.00 c.c.	1.20 c.c.
2	18	1.00 c.c.	9.60 c.c.
12	19	1.00 c.c.	7.90 c.c.
16	20	1.00 c.c.	9.75 c.c.
17	20	1.00 c.c.	10.80 c.c.
22	21	1.00 c.c.	8.92 c.c.
23	22	1.00 c.c.	8.50 c.c.
25	22	1.00 c.c.	12.35 c.c.
27	24	1.00 c.c.	14.40 c.c.
28	24	1.00 c.c.	11.50 c.c.
29	24	1.00 c.c.	7.85 c.c.

It is also evident from this study that the clinical end-results from pollen therapy do not always depend upon the total amount of pollen administered in each case, a point emphasized by Rackemann[2] although not upheld by Brown[3] who found that the higher doses are productive of better clinical end-results. Thus in our five ragweed cases where complete relief was noted, the total amounts of 1:500 pollen extract administered are shown in Table III.

TABLE III

CASE NO.	TOTAL AMOUNT OF POLLEN IN 1:500 DILUTION
1	2.50 c.c.
2	9.60 c.c.
3	3.15 c.c.
4	15.35 c.c.
5	2.75 c.c.

Against these figures we have several patients with only slight relief who received even larger total amounts than some of the above cases (Table IV).

This detailed analysis indicates that the number of doses bears no relationship to the clinical end-results in pollen therapy and that the size of the final dose and the total amount of pollen administered do not parallel the degree of clinical relief obtained. Hence we may conclude that no

TABLE IV

CASE NO.	TOTAL RAGWEED IN 1:500 DILUTION	TOTAL GRASSES IN 1:500 DILUTION
33	9.85 c.c.	0.00 c.c.
41	13.20 c.c.	6.15 c.c.
42	4.45 c.c.	0.60 c.c.

preformed schedule of doses can be accepted as suitable in any given instance.

Certain failures in pollen therapy have been explained on the basis of multiple sensitization as recently emphasized by Kern,[4] Vaughan[5] and others. In this group of 44 patients, a sensitivity to substances other than, and in addition to, pollen was found in 19 of the ragweed cases, in all of the 8 ragweed and grass cases and in one of the two grass pollen cases, altogether 28 out of 44, or about 64 per cent.*

In Table V we see a comparison of the end-results in therapy between patients with multiple sensitivity and those with pollen sensitivity only.

TABLE V

A COMPARISON OF THE END-RESULTS IN THERAPY BETWEEN PATIENTS WITH MULTIPLE SENSITIVITY AND THOSE WITH POLLEN SENSITIVITY ONLY

	NO. OF CASES	RELIEF			
		COMPLETE	MARKED	SLIGHT	NONE
Ragweed Cases					
Multiple sensitivity	19	2	15	1	1
Pollen sensitivity only	15	3	12	0	0
Combined Ragweed and Grass Cases					
Multiple sensitivity	8	0	5	2 1 to grass	0
Pollen sensitivity only	0	0	0	0	0
Grass Cases					
Multiple sensitivity	1	0	1	0	0
Pollen sensitivity only	1	1	0	0	0

No striking conclusion can be drawn from this analysis, although we note that complete relief was more common in cases with pollen sensitivity only, whereas our failures fall exclusively into the group with multiple sensitivity. On the other hand, in the group of "marked relief" we have 21 instances with multiple sensitivity as against 12 with pollen sensitivity alone. We may, therefore, conclude that multiple sensitivity, as far as could be determined by the history of the cases in this group and the

*All patients in this group were tested with twenty or more allergens including common foods, animal emanations, orris, pyrethrum and dust.

limited number of tests performed, may, in occasional instances, only influence the end-results in pollen therapy.

Several patients in this group who had failed to benefit from treatment elsewhere gave a history of large local reactions in former years. This prompted us to aim for smaller reactions in all the members of this group, and we therefore lack a suitable number of cases with large local reactions for comparative study. Our observations, however, indicate that small local reactions are not inconsistent with good therapeutic results and that poor results may concur with large reactions.

Certain patients who are refractory to treatment tend to resist even a slight increase in dosage and have painful reactions at the site of inoculation. In such instances we found it practicable to repeat the same dose daily on alternating sites until all evidence of reactivity ceased. It then became easier to advance the dose cautiously as treatment progressed. Here, again, emphasis must be brought on the fallacy of estimating, a priori, not only the size of each subsequent dose but also the intervals between the doses.

COMMENT

The treatment of hay fever, though widely practiced by the use of the so-called twelve or twenty dose schedule, is in reality an intricate procedure. The factors that enter into the evaluation of each case are manifold. It is evident from our observations that individualization of patients, a point stressed by Rackemann, is of paramount importance if good results from therapy are to be expected. It is true that an occasional patient may need as many as fifty inoculations, but these are the uncommon instances and represent the refractory type who may have failed in the attempt to gain protection from the traditional twelve to twenty doses.

If, as follows from this study, the number of doses, the size of the final dose and the amount of pollen needed in each case are uncertain quantities which cannot be estimated a priori, the question then arises, how shall the treatment of hay fever be carried out?

In the present state of our incomplete knowledge of the mechanism of desensitization, it is rational to accept the following three important guides in pollen therapy: first, the extent of the dermal reaction to serial dilutions of the offending pollen in determining a safe initial dose; second, the extent of the local reaction from each inoculation as a guide in estimating a second dose; and third, the change in the dermal reaction as treatment progresses, as an index of the patient's changing tolerance for pollen.

This triad is fundamental and represents the sine qua non in the management of hay fever patients. The last one of the triad recently described[1] has become an invaluable aid in the management of the individual

patient, since it enables us to disregard any preformed schedule of doses in favor of the phenomenon of lessened sensitivity as manifested by the diminution of, or extinction of a previously positive test.

Occasionally a patient fails to obtain clinical relief in spite of the disappearance of a formerly positive dermal reaction, in which case we are dealing either with other sensitivities or with an extremely sensitive shock organ which responds violently, not only to immunologically specific irritants but to unrelated and nonspecific offenders as well. Such states obtain in old-standing cases of patients who sneeze more or less all year round from such diverse stimuli as odors of all kinds, changes in temperature, house dust and wet feet, even as they do from contact with the specific pollen.[6] Here the problem is much more complicated and calls for more than the injection of a number of pollen doses. The patient as a whole may be below par, debilitated, anemic and in need of proper dietary and medicinal measures to restore his normal well-being. The nasal mucosa may be edematous and avascular even before the onset of the hay fever season. Here, elimination of other sensitivities and local treatment of the shock organ may pave the way for better therapeutic results.

With all that, not every patient, no matter how well treated, can be relieved from hay fever by pollen therapy, no more than every luetic can be cured by the administration of salvarsan. Refractoriness to therapy, as pointed out by Cohen, et al.,[7] is frequently met with in any therapeutic procedure. Such intricacies of resistance have much to do with the very fundamentals of the biologic processes in man, in health as well as in disease, which, when cleared, may open a new approach to diseased states in general.

CONCLUSIONS

1. The treatment of pollen disease is a complicated process which entails more than the mere administration of some twelve to twenty pollen doses.

2. Neither the number of doses, the size of the last dose, nor the total amount of pollen needed, can be, a priori, estimated in any given case.

3. The phenomenon of changing sensitivity as determined by repeatedly titrating the patient's skin with serial dilutions of the offending pollen is suggested as a guide in the treatment of pollen disease.

4. Emphasis is brought on the individualization of patients as the key note in successful pollen therapy.

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371 COMMONWEALTH AVENUE.

THE RAGWEED SEASON OF 1932*

In the United States, Canada and Mexico

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THIS is the fourth[1, 2, 3] of a contemplated series of five consecutive annual atmospheric ragweed pollen studies. Some of the purposes of the five-year survey are to establish the boundaries of the effective ragweed district of North America, to compare the severity of pollen incidence in various sections, to determine the average local dates of onset, crisis and

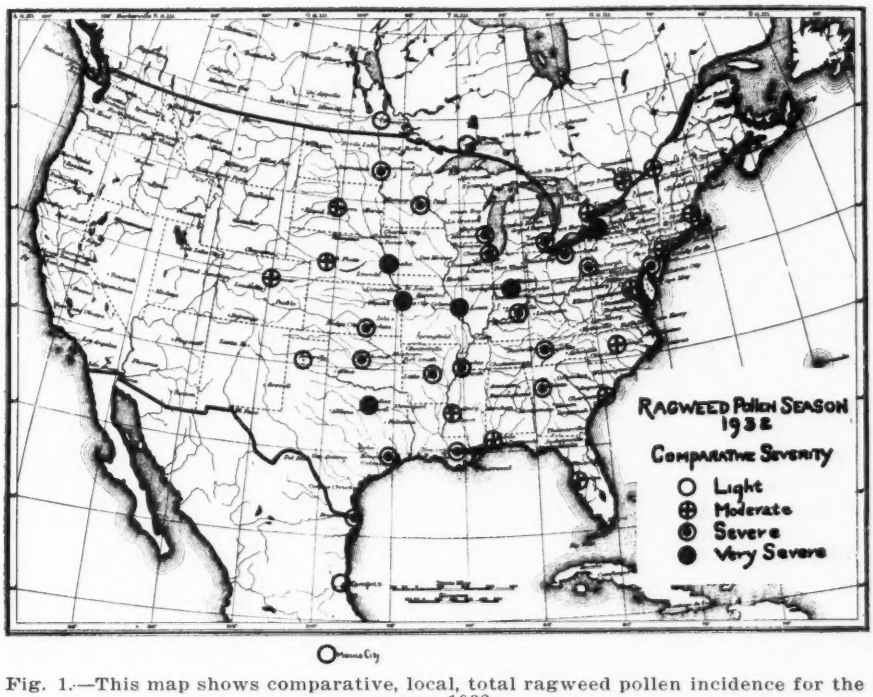

Fig. 1.—This map shows comparative, local, total ragweed pollen incidence for the season 1932.

termination of the ragweed season, and to learn as much as possible about the local and general factors affecting the production and distribution of ragweed pollen. The 1932 study involved the exposure of 43 series of slides at locations shown in Fig. 1, and the systematic examination of nearly 2,700 slides. As in previous studies, the exposures were made under uniform conditions and with uniform apparatus at the stations of the U. S. Weather Bureau† and the Canadian Meteorological Service.†

*From the Biological Laboratories of Abbott Laboratories.

†Grateful acknowledgement is again made of the valuable cooperation of the U. S. Weather Bureau observers through the courtesy of their chief, Dr. Charles F. Marvin; also, of the kind assistance of the observers of the Canadian and Mexican Meteorological Services, through their directors, Dr. J. Patterson and Sr. Alfonso Contreras Arias, respectively.

TABLE I

ANNUAL RAGWEED POLLEN RECORDS

CITY	APPROXIMATE LENGTH OF SEASON IN DAYS	1929	1930	1931	1932
Amarillo	40	....	....	98	163
Atlanta	43	1437	1284	2408	3243
Boise	27	332	....	....	....
Boston	26	582	707	1169	796
Brownsville	105	....	....	3496	2042
Buffalo	35	4202	3948	14675	12386
Charleston	45	....	....	373	716
Chicago	35	4132	3046	5018	6020
Cleveland	35	3214	2646	5184	4892
Dallas	54	4634	2569	3606	8176
Denver	37	1767	675	965	1059
Detroit	35	....	2193	3901	5547
El Paso	30	110	....	....	....
Houston	46	....	5278	4055	6070
Indianapolis	40	11439	7115	9998	14409
Jacksonville	75	....	205	....	....
Kansas City	50	12806	4055	5492	9187
Knoxville	41	....	2782	3254	4008
Little Rock	50	....	....	2024	2776
Los Angeles	30	32	....	....	....
Louisville	46	....	3934	11355	6438
Memphis	50	4580	2977	3623	5112
Mexico City	?	....	....	....	39*
Miami	0	8	....	....	....
Miles City	15	248	....	....	....
Milwaukee	35	....	....	7458	5073
Minneapolis	45	....	2596	3674	6984
Mobile	60	....	....	228	507
Montreal	28	....	439	740	806
Moorhead	33	6267	3501	3946	3995
New Orleans	66	1090	1982	1350	2533
New York	31	1196	1100	2643	1451
North Platte	30	....	722	372	831
Oklahoma City	56	6309	3360	3115	3306
Omaha	50	12085	3790	5936	11207
Ottawa	28	....	....	459	623
Philadelphia	40	1799	2040	3514	2185
Pierre	30	....	388	313	1199
Pittsburgh	35	2499	1828	5734	2756
Port Arthur	14	....	....	226	378
Prince Albert	0	....	6	....	....
Raleigh	35	557	929	1786	1078
St. Louis	46	5686	3487	5573	8619
Salt Lake City	33	....	313	....	....
Sault Ste. Marie	26	500	....	....	....
Seattle	0	0	....	....	....
Tampa	50	....	....	582	636
Tampico	?	....	....	....	279*
Toronto	35	....	581	1357	1600
Vicksburg	50	....	....	1355	1528
Washington	46	1956	1241	3933	1497
Wichita	59	10123	3979	4009	6406
Winnipeg	14	....	130	252	278
Total		....	....	140,249	158,416

*Not included in averages and totals.

In addition, I have had this year the cooperation of the Mexican Meteorological Service† at its weather stations at Tampico and Mexico City.

METHOD

The method of exposure (the so-called "gravity method"), the technic of counting and the method of expressing the results are the same as in the three previous studies. I have admitted[4] that the gravity method of obtaining quantitative samples of the atmospheric pollen content is not extremely accurate, but it is the only known method that could possibly be adapted to an inquiry of such wide extent. Its practical value should not be judged theoretically, but by the consistency of the results obtained. Repeated local clinical records[5, 6, 7] of hay fever suffering attest to the accuracy of this method of measuring the fluctuations of the pollen content of the air. Attention is again called to the fact that conditions of exposure are identical in almost every detail in each of the 43 stations, and that there is no change from year to year.

TOTALS

The total amount of ragweed pollen found on all slides (Table I) during 1932 was 13 per cent in excess of the amount found in 1931 and is the largest for any of the four years. This increase was not due to a few very high local records but was uniform throughout the United States and Canada, with the exception of the eastern states, whose unusually heavy record of last year was not duplicated. Indianapolis produced the highest count for one day and the highest total of any station in this year's study—almost equalling the Buffalo figures for last year. The lowest local record was obtained at Mexico City.

THE SEASON

The season began early. In most places toxic concentrations were reached a week earlier than usual. The season commenced in the north about August 13 and in the south about September 1. It will be noticed on the mean graph (Fig. 2) that during the first three weeks the curve is almost 100 per cent above that of the previous year. Extreme concentrations were reached somewhat earlier than usual and continued for almost two weeks, the average apex occurring on September 1. During the latter part of the season the curve was only slightly higher than in previous years. At Pierre, South Dakota, the worst pollen day was August 22—fifty days earlier than the apex at Brownsville on October 11.

THE WEATHER

Total wind movement during the active ragweed season at twenty-one key stations was about 10 per cent higher than that for any of the preceding three years. This helps to explain the uniform increase in the total pollen count. Rainfall during June, July and August, except on the east-

ern seaboard, averaged more than last year. Thus, the two most important weather factors combined in producing and distributing the largest recorded ragweed pollen crop. Total summer rainfall in all the cities being studied has in none of the four years been more than normal. We have had, then, three years of average summer rainfall and one severe drought (1930). A few unusual local pollen records have been encountered in these years, but it is quite certain that a much heavier total pollen crop can be produced with heavier average summer rainfall throughout the Mississippi Basin than has been experienced in these four years. Generally, our severe pollen winds, except on the coast, are from the south or southwest. Thus, the southern states are usually free from large amounts of ragweed pollen during the first three weeks of the season. But this year our high winds were mostly from the north. On August 18 a strong north wind blew down the Mississippi Valley, not only causing a heavy

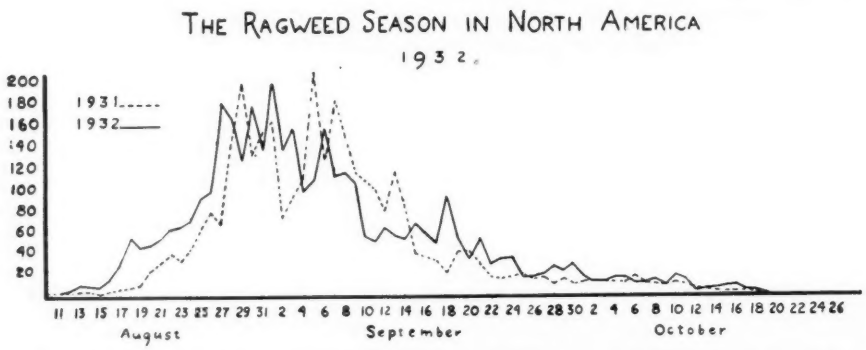

Fig. 2.—These mean curves are plotted from daily averages of pollen incidence in all stations in the United States and Canada. The totals for the two stations in Mexico are not included on account of lack of previous records. Figures represent calculated number of ragweed pollen granules per cubic yard of air.

fall of pollen in most northern cities, but apparently carrying moderate quantities as far as Memphis and Little Rock. The mean apex of September 1 was partly caused by north winds in Missouri, Illinois and Indiana; and on September 6, a northwest wind swept the southeastern United States, giving most of the stations in that area their worst day. How much pollen was actually shifted for long distances into the south is a matter of conjecture, but the effects of the wind are easily traced from St. Louis to the southeastern seaboard and the Gulf.

LOCAL COMMENT

Canada (Toronto, Montreal, Ottawa, Port Arthur, Winnipeg) (Fig. 3).—The figures were somewhat higher at all five Canadian stations than heretofore. Toronto, which is farther south than Minneapolis, has considerably more pollen than any of the other cities, but the amount is still small compared with that of Buffalo, the nearest city in the United States. There is some evidence that part of Toronto's pollen is blown across the

lake, or at least from southwest Ontario. Port Arthur had only one really bad day—August 30. The slide for that day was otherwise clean, the wind was off the lake, and prevailing winds over all Wisconsin were from the south. These facts suggest that most of the pollen found at Port Arthur on August 30 was blown from across Lake Superior. As would be

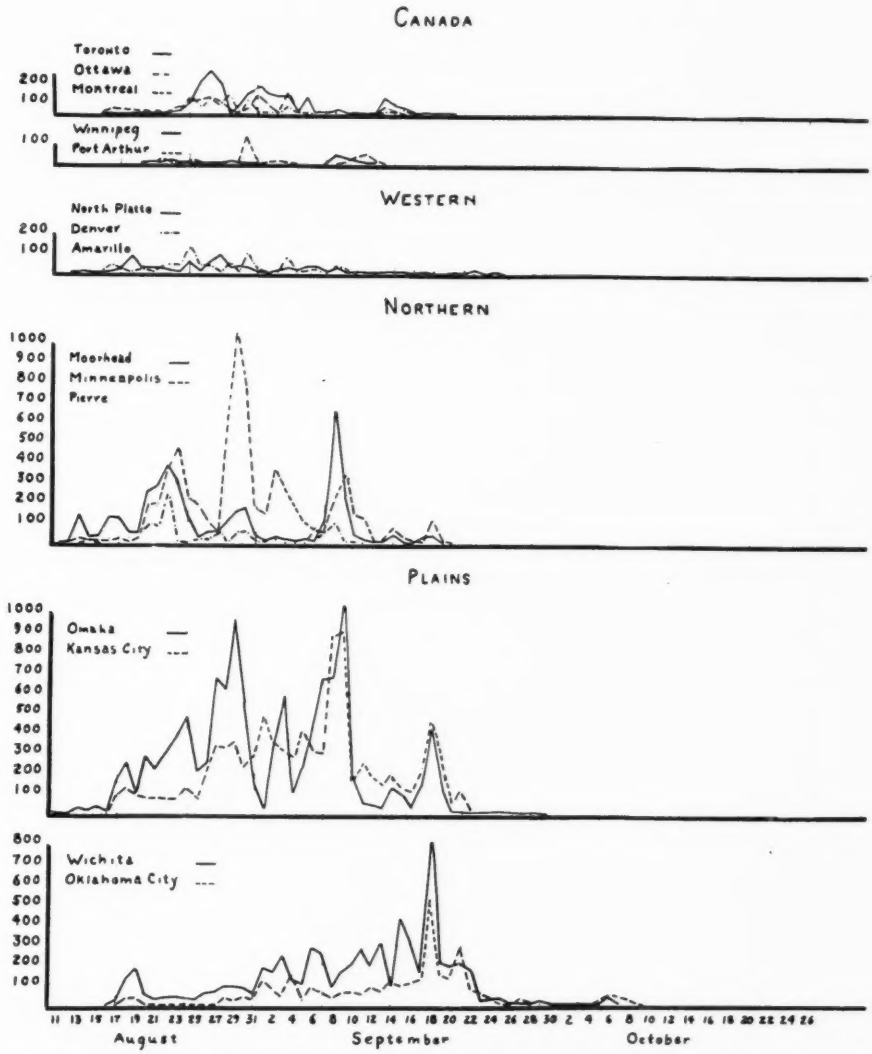

Fig. 3.—Ragweed pollen season of 1932. Figures represent calculated number of ragweed pollen granules per cubic yard of air.

expected, there is some resemblance between the curves for Ottawa and Montreal.

Western (Denver, North Platte, Amarillo) (Fig. 3).—This group of stations west of the hundredth meridian might well have included Pierre. All had more pollen than last year, but the amount at Amarillo is still in-

significant—less than any other station on this year's list except Mexico City. This would be a good hay fever resort if only ragweed were considered. Rainfall in western Kansas, western Nebraska and Colorado was greater than in 1931, but still not up to normal. While concentrations in North Platte were not heavy, the season was really quite long compared with other western and northern localities.

Northern (Moorhead, Pierre, Minneapolis) (Fig. 3).—The fluctuations of the three curves in this group are quite similar; although they were much exaggerated at Minneapolis between August 27 and September 6. The effect of weather factors over a wide area could have no more striking illustration than that afforded by the correlation of these three curves during the third week of August and the second week of September.

Plains (Omaha, Kansas City, Wichita, Oklahoma City) (Fig. 3).—Summer rainfall in this area was not at all uniform. Oklahoma City had heavy rains, but the condition was decidedly local. In the Omaha area there was also an excessive amount of rain. In both these places there was not only a heavy ragweed crop, but also an unusually heavy crop of other fall pollens. In fact, in both places ragweed pollen constituted less than one-half of the total pollen content of the air. Note the effect of the wind storm (from the south this time) of September 18 in all four of these cities. Again the long season at Wichita and Oklahoma City is noteworthy.

Eastern (Boston, New York, Philadelphia, Washington) (Fig. 4).—This district received less than half the amount of summer rainfall experienced in 1931, which easily accounts for the fact that the amount of pollen in these four cities dropped to about half that of the former year. Clinical experiences of allergists in this district agree with these findings.

Great Lakes (Buffalo, Cleveland, Detroit, Chicago, Milwaukee) (Fig. 4).—The Great Lakes cities experienced the usual severe, but comparatively short—five weeks—ragweed season. Rain interfered seriously with pollination only at Detroit on August 29. Milwaukee had less pollen than last year.

Mississippi Valley (St. Louis, Memphis, Little Rock, Vicksburg) (Fig. 4).—Excessive summer rainfall at St. Louis produced its largest recorded pollen crop. There was, however, as heretofore, no tendency for the season to continue after September 20. I have no explanation for the fact that the St. Louis ragweed season occurs at practically the same time as the Chicago season, and is wholly unlike that at Memphis, whereas there is as much difference in latitude between St. Louis and Chicago as between St. Louis and Memphis. The graph shows the effect of the wind storm of August 18 on Memphis and Little Rock. My suggestion that the north wind on this date blew pollen into the south is confirmed by field observations of Dr. J. P. Henry of Memphis, who says that at that time the local ragweeds were not sufficiently mature to be responsible for the atmospheric findings.

Ohio Valley (Pittsburgh, Indianapolis, Louisville) (Fig. 5).—The Indianapolis curve is higher than that of 1931, while those of Louisville and Pittsburgh are lower. These stations all show the effect of the north wind of August 18.

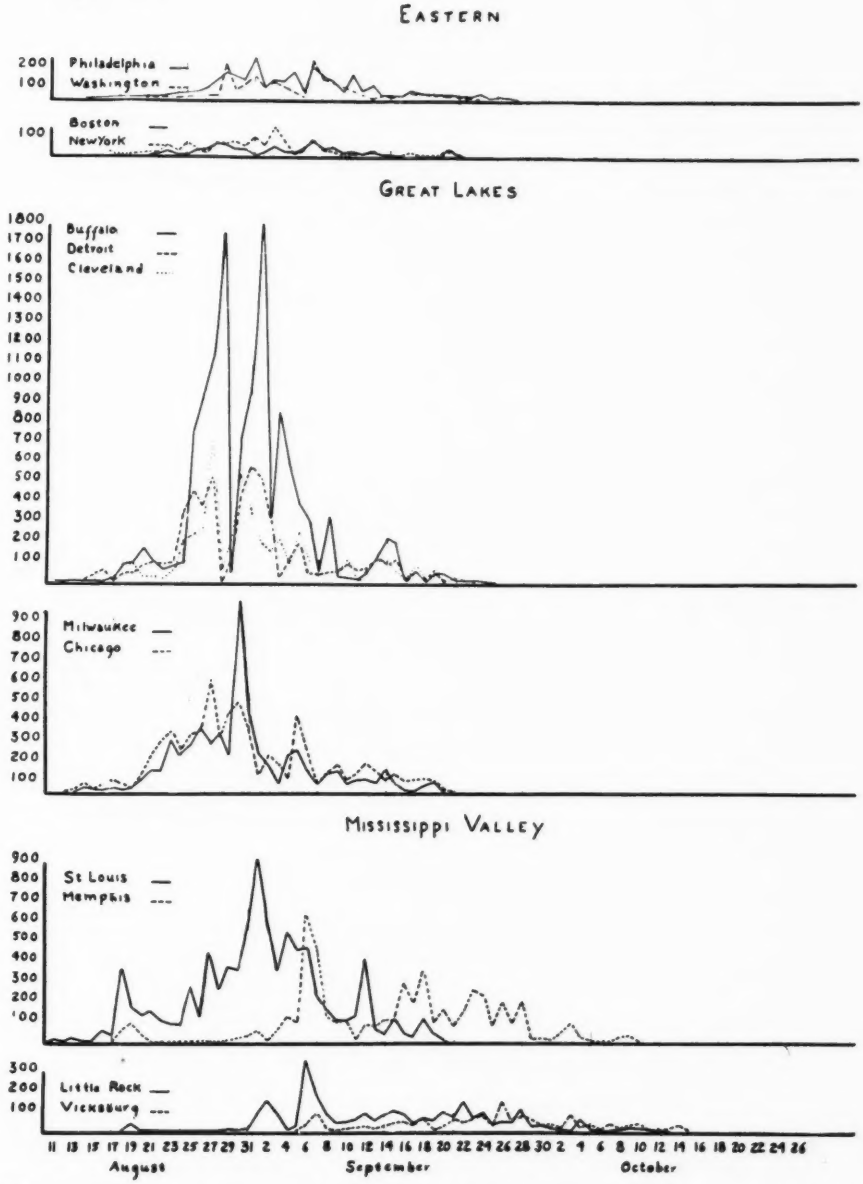

Fig. 4.—Ragweed pollen season of 1932. Figures represent calculated number of ragweed pollen granules per cubic yard of air.

Southeastern (Knoxville, Atlanta, Raleigh, Charleston) (Fig. 5).—The curves are strikingly similar and very much like those for Memphis, Little Rock and Vicksburg. In each of these four cities the apex of pollen inci-

dence was caused by the northwest wind of September 6 and 7. All except Raleigh had more pollen than in 1931. Raleigh was short on summer rainfall, like Boston, New York, Philadelphia and Washington.

Texas (Dallas, Houston, Brownsville) (Fig. 5).—Amarillo is not in-

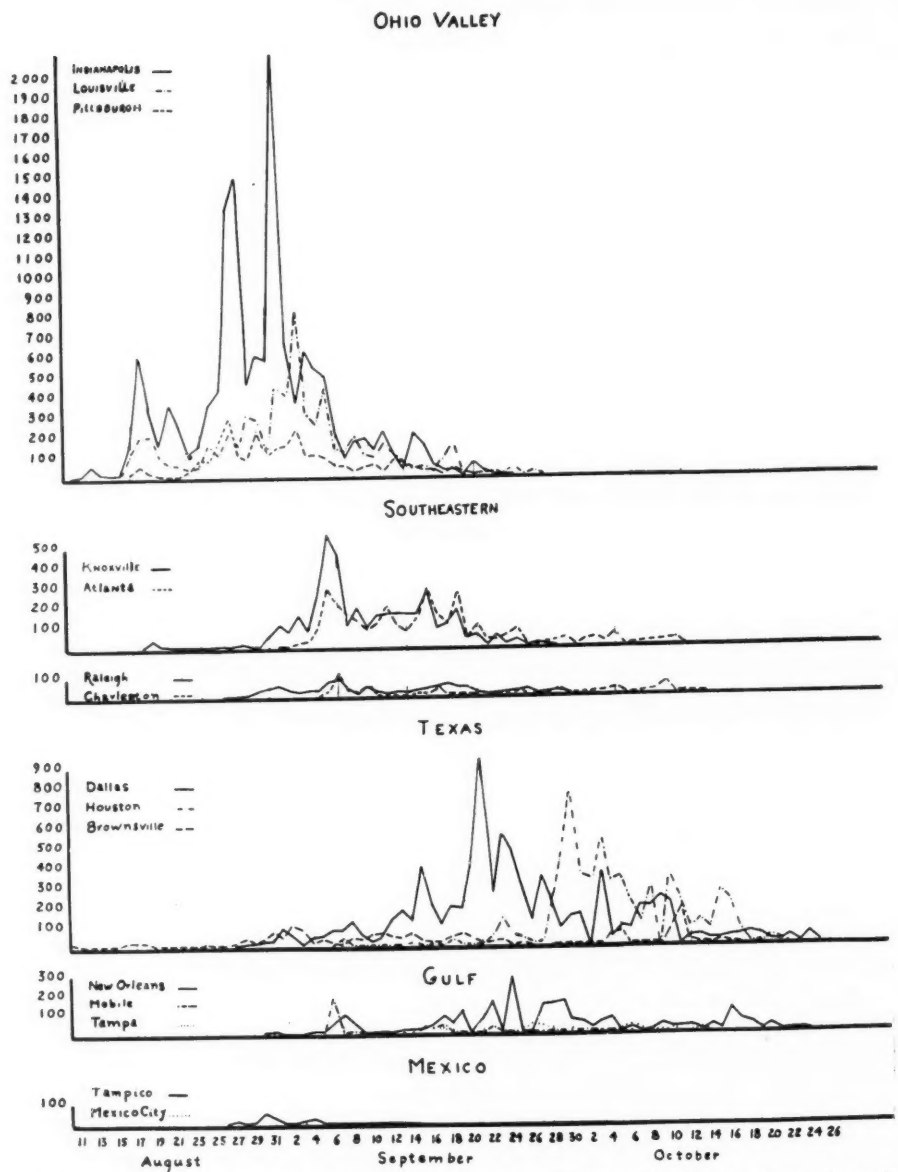

Fig. 5.—Ragweed pollen season of 1932. Figures represent calculated number of ragweed pollen granules per cubic yard of air.

cluded in this group as it is so much nearer Colorado than central Texas. This is the heaviest record for Dallas, where summer rainfall was still considerably under normal. At both Dallas and Houston the crest of the

pollen storm was caused by east winds. East Texas seems to be the ragweed capital of the south. As noted last year, the picture at Brownsville differs widely from that of any other southern locality. Instead of a definite, late season beginning about September 1, as in Houston or New Orleans, the season begins even earlier than that in Canada or in the mile-high area of Denver. Western ragweed (*Ambrosia psilostachya*) begins to pollinate at Brownsville as early as the last of May and at least one other species is in full bloom by August 1. There is then pollen until November 1—probably later. So the limits of the "season" are still undetermined.

Gulf (New Orleans, Mobile, Tampa) (Fig. 5).—Of the three cities in this group along the east Gulf coast only New Orleans has enough pollen to cause serious trouble. If Mobile and Tampa were farther from the water, their ragweed problem would probably be more serious. Pollen seems to blow into Mobile only on strong north winds. Fortunately, there was only one such wind this year. The pollen curves for Mobile and Tampa are very similar to the curve for Charleston, the only other seacoast station in the south.

Mexico (Mexico City, Tampico) (Fig. 5).—These two new stations were added in an effort to supplement our information about the southern limits of the ragweed area. The arrangements for exposures were not completed in time to begin as early as desired. Slides were exposed from August 24 until October 31—just in time to check with Brownsville's record. The Tampico curve follows the Brownsville curve only from August 27 to September 4, after which time there was very little pollen on the slides. The Tampico total is the same as that of Winnipeg. Mexico City is our "farthest south"—1,700 miles south of Winnipeg. The pollen catch was very meager. Conditions are probably somewhat similar to those in the plateau region of the western states, where the moisture is insufficient for the common, heavy-pollinating ragweeds.

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THE IMPORTANCE OF MOLDS AS ALLERGIC EXCITANTS IN SOME CASES OF VASOMOTOR RHINITIS

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IT HAS been gratifying to note the increasing interest with which molds are being regarded by allergists. The importance of molds in the production of pathologic lesions of the internal organs and of the skin has long been recognized. The concept, however, that molds may act as allergic excitants, giving rise to a disturbance in function, is of recent origin. Our case of asthma due to *Aspergillus fumigatus* may well serve as an illustration. This mold was responsible for severe asthma in a woman for a period of over nine years. Repeated physical examination made by competent physicians and supplemented by radiographic examinations failed to reveal any focus of infection. The same mold has often been found to be the cause of aspergillosis in birds. In man, pulmonary infections with *Aspergillus fumigatus* closely resembling tuberculosis both clinically and pathologically have been extensively reported in the literature.[1]

In 1923, cutaneous testing with mold reagents was initiated in our practice. In 1924, Van Leeuwen[2] and Cadham[3] reported that molds and wheat rusts were excitants of the asthmatic state. In 1928, Hansen[4] of Heidelberg published his observations that extract of molds yielded positive skin reactions in 15 per cent of his asthmatic patients. In this country in January, 1930, Hopkins, Benham and Kesten[5] of Columbia University College of Physicians and Surgeons were the first to report a case of asthma due to a fungus, *Alternaria sp.* This was followed six months later by our case of asthma, caused by sensitization to *Aspergillus fumigatus* to which reference has been made.[6] Other observers, both in this country and abroad, have since confirmed the importance of molds as potential factors in asthma. Accordingly, the scope of specific therapy has been enlarged in a proportion of asthmatics who otherwise would have been classified as nonreactors.

In contrast with these asthmatic cases in which molds play an important rôle, we desire to report a series of cases of certain types of vasomotor rhinitis in which molds are likewise the sole or contributory excitants. It is noteworthy that all the patients who comprise the series have been previously studied by rhinolaryngologists. The absence of any definite pathology and the lack of response to the usual local treatments prompted

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further investigation. Our thanks are due to the several colleagues who have made the study possible by kindly referring these patients to us.

The series can readily be divided into two groups. In the first group, the most prominent and distressing symptom was stuffiness of the nose which affected either one or both nostrils. This symptom was constant and was only occasionally accompanied by paroxysmal sneezing and a scant coryza. Examination in this group revealed the pale and boggy enlarged turbinates.

In the second group the symptoms were typical of perennial hay fever. Paroxysmal sneezing and a profuse coryza were the chief causes of distress. Itching of mucous membranes, lacrimation, and stuffiness of the nose added to the discomfort.

Each patient in the two groups was routinely tested by the cutaneous method with representative pollens, epidermal and miscellaneous proteins, food proteins, and molds. It may not be amiss to present a clinical summary of the patients.

GROUP I

CASE 1.—Male, aged twenty-nine years. Duration of disease ten years. Age at onset nineteen years. Chief complaint—"head stuffs up" and was acutely so for three weeks prior to first visit. The molds, *Alternaria* and the McCammon *Trichophyton* yielded positive skin tests. He was under observation and treatment from April 14, 1930, to November 3, 1930.

CASE 2.—Male, aged seven years. Duration of disease one and one-half years. Age at onset five years. Chief complaint—stuffiness of nose and paroxysmal sneezing. Slight itching of nose occurred only during a paroxysm of sneezing. The mold, *Alternaria*, proved to be the sole reacting allergen. He was treated by applications of the powdered mold material to scratch marks on the forearm from September 9, 1930, to October 24, 1930. When an extract of the *Alternaria* was made available, a course of desensitizing treatments was begun on November 18, 1930, and terminated on May 8, 1931.

CASE 3.—Male, aged forty years. Duration of disease one year. Age at onset thirty-nine years. Chief complaint—"has had a hard job to breathe through the nose. The nostrils are alternately swollen." In November, 1930, operation for deviated septum was performed. He experienced complete relief from symptoms for two months following the operation. Symptoms then recurred and were most aggravated. The stoppage of nose interfered with sleep and necessitated mouth-breathing. Cutaneous testing revealed a sensitiveness to the McCammon *Trichophyton* and to the pollens of the short and giant ragweeds. He was given a course of desensitizing treatments with an appropriate mold extract from April 27, 1931, to June 1, 1931. This was followed by five injections of a combined ragweed pollen extract after which the patient discontinued treatment.

It is noteworthy that the subcutaneous injections of the pollen extract provoked no localized reaction.

CASE 4.—Male, aged twenty-five years. Duration of the disease two years. Age at onset twenty-three years. Chief complaint—"marked stuffiness of nose. The nasal discharge runs back instead of forward. Sneezing not any more than normal." Tonsillectomy, adenectomy, and turbinectomy were performed at the age of eight years. The patient is underweight and is susceptible to colds. The McCammon *Trichophyton* proved to be the only positive reacting allergen. He was under treatment from February 17, 1931, to September 3, 1931.

GROUP II

CASE 1.—Male, aged twenty years. Duration of disease ten years. Age at onset ten years. Complaints—perennial sneezing, worse during the spring and summer months, itching of mucous membranes, profuse coryza, lacrimation, eyes sensitive to light, occasional stuffiness of nose. In addition he is susceptible to colds. Because of his sensitiveness, which was subsequently determined, his statement that moldy odors are unpleasant to him and that they provoke sneezing and make him feel as if he has a cold, becomes significant. In a comprehensive list of test reagents, the following gave markedly positive reactions: the pollen of sheep sorrel, *Alternaria,* the McCammon *Trichophyton, Aspergillus glaucus* and the kernel smut of sorghum. He was given an intensive course of treatment from July 1, 1930, to September 24, 1930.

CASE 2.—Male, aged sixteen years. Duration of disease eight years. Age at onset eight years. Chief complaint—extreme stuffiness of nose making nasal breathing difficult. Other typical symptoms of hay fever were also present. The symptoms were perennial and unaffected by seasons. They first appeared when the patient was resident in the West Indies, and persisted during his migratory career in China, Japan, the Philippine and Hawaiian Islands. He arrived in Washington, September, 1929, after a stay in Long Beach, California. He was first seen by me on September 19, 1930. The following allergens yielded positive skin reactions: the pollens of June and sweet vernal grass, the pollens of the short and giant ragweeds, *Aspergillus flavus, Aspergillus terreus, Polyporus versicolor,* and *Alternaria.* After a series of subcutaneous tests with extracts of the above positive reactors, to which reference will be made later, a course of desensitizing treatments with an extract of *Alternaria* was administered. The course covered the period from December 3, 1930, to March 28, 1931. It is noteworthy that a constitutional reaction, similar to that seen in the administration of pollen extract, followed one injection of the mold extract and was readily controlled by the use of adrenalin.

CASE 3.—Male, aged seventeen years. Duration of the disease five

years. Age at onset twelve years. Complaint—perennial hay fever, accompanied by two asthmatic attacks. The stuffiness of nose is of moderate degree and is present more or less throughout the year. His first attack of asthma occurred while on a steamer crossing the Atlantic ocean. It was of four hours' duration. The second asthmatic occurred four days prior to his first visit to us, on September 20, 1930. On testing, he manifested a skin sensitiveness to the pollens of the grasses, the pollen of the short ragweed, and to *Alternaria.*

CASE 4.—Female, aged sixteen years. Duration of the disease ten years. Age at onset six years. Complaint—perennial hay fever, aggravated, however, from the latter part of August until October 1. During the past two years, asthmatic complications have appeared during the fall and winter months. The pollen of the short and giant ragweeds and the mold, *Alternaria,* proved to be the only positive reacting allergens in a comprehensive list of test materials. This patient was under treatment for three weeks, from November 26, 1930, until December 17, 1930, at which time she moved from the city.

A review of the eight patients cited above, indicates a predominance of males, there being one female in the list. The youngest in the series was seven years and the oldest forty years of age; whereas, the duration of the disease varied from a minimum of one year to a maximum of ten years. It is significant that three patients, or 37.5 per cent, have reacted exclusively to the molds. These would have been classified as "nonreactors" if testing with mold material had been omitted. In other words, they might have been "missed cases." The remaining four patients, or 62.5 per cent, reacted positively not only to the mold allergens, but also to the more common pollens of the grasses and of the ragweeds. In this latter group, the question naturally arises as to which of the reacting agents was the exciting etiologic factor. An analysis of the clinical data furnishes important criteria. Thus, in Patient No. 2 in the series with perennial hay fever, his symptoms were unaffected by seasons. They were present during his residence in the Far East where the ragweeds do not flourish despite his positive skin reactions with their pollens. Likewise, Patient No. 3 in the same series, was subject to perennial manifestations. Nevertheless, there was no aggravation of his distress when he drove in an automobile across the United States during the summer of 1930. The inevitable exposure to massive doses of pollens on such a trip should have provoked marked exacerbation of his symptoms; for it will be recalled that he manifested a skin sensitiveness to the pollens of the grasses and of the ragweeds. The clinical considerations, in these cases at least, point to causes other than the common pollens.

There remains, however, a clinical test which is of decisive value in the solution of the problem presented. The earlier investigators in hay fever have only too well appreciated the multiplicity of skin reactions which

were obtainable in hay fever subjects and especially the cutaneous reactions with pollens which do not initiate seasonal clinical disturbances. For purpose of convenience we have termed these "secondary or accessory reactions." We quote some of the conclusions drawn from a previous study of this phase of the subject:[7]

"Cutaneous and intracutaneous and mucous membrane sensitiveness to pollen protein are three distinct entities. Cutaneous sensitiveness may be present in individuals who do not exhibit mucous membrane sensitiveness to the same pollen. The subcutaneous reaction to pollen protein is a more critical and specific index of mucous membrane sensitiveness than the cutaneous or intracutaneous tests."

In accordance with this deduction, which time and experience have confirmed, a series of subcutaneous tests was performed in each patient to determine the specific offending allergen. This was a fundamental prerequisite for therapy in five of the patients in whom the phenomenon of multiple cutaneous sensitiveness was present. Accordingly, minute doses of mold extracts and of pollen extracts were on different occasions injected subcutaneously in the upper arms. The allergens which gave rise to positive subcutaneous tests were regarded as the specific offenders. A positive subcutaneous reaction is characterized by a diffuse swelling at the site of injection, accompanied with a redness and a sensation of heat and itching.

The above series of tests indicated that one patient was sensitive to *Alternaria* and the McCammon *Trichophyton*; three patients were sensitive to *Alternaria*; three to the McCammon *Trichophyton*; and one to *Alternaria* and the pollens of the ragweeds. The patient found sensitive to *Alternaria* and to the ragweed was case No. 4 in Group II. Her symptoms were those of perennial hay fever and were aggravated from the latter part of August until October 1. The clinical tests were confirmatory of the clinical picture. By way of contrast, Case No. 3 in Group I, exhibited a cutaneous sensitiveness to *Alternaria* and to the pollens of the ragweeds. His symptoms were likewise perennial but were unaffected by seasons. A positive subcutaneous reaction was elicited with an extract of *Alternaria;* whereas five injections of gradually increasing doses of mixed ragweed pollen extract provoked no local reactions.

The extracts of mold were prepared in a manner similar to that of pollen extracts. The dried pellicles were ground in mortar and pestle and were extracted with a solution consisting of one-third Coca's solution and two-thirds of glycerin.

The initial dose of mold extract consisted of 0.05 c.c. of a dilution 1:10000. For purpose of control 0.1 c.c. of the extracting fluid was injected in the other arm at the same time.

It is noteworthy that of the various mold agents employed in testing, only two, *Alternaria* and the McCammon *Trichophyton,* were found re-

sponsible for the types of vasomotor rhinitis described above. Credit is due Hopkins, Benham and Kesten of Columbia University for their valuable contributions which have added *Alternaria* to the list of possible causes of asthma. This mold is commonly present in house dust. The constancy and universality of species of *Alternaria* readily explain the perennial character of the symptoms which they are capable of exciting at all times and in all parts of the world. This is exemplified in Case No. 2 of Group II. This young patient, it will be recalled, had extreme stuffiness of the nose for a period of eight years in the West Indies, China, Japan, the Philippine and Hawaiian Islands, California, and the District of Columbia.

The McCammon *Trichophyton* represents the growth obtained from an ulcerating lesion of the foot. The culture was submitted to us by Mrs. Ruth N. McCammon of Cincinnati, to whom we express our indebtedness, and was identified by Doctor Margaret B. Church, then working at the Vanderbilt Clinic. Subculturing ultimately revealed the presence of two organisms, a white *Actinomycete* and a *Trichophyton*. These were isolated in pure culture, and the *Trichophyton* was determined to be the active allergen.

The *Trichophyta* are well known parasites of the integument of man and of the warm-blooded animals. They produce ringworm of the scalp and are responsible, also, for a variety of lesions of the glabrous skin, beard and nails.[8] The genus, according to Sabouraud, consists of about thirty species.

The many cases of infection with *Trichophyton* which are present in our population provide a reservoir of allergenic material for those individuals who develop sensitiveness. Sensitiveness in man implies a peculiar response to an environmental factor with which the subject is not in harmony. It will be interesting to see what percentage of those clinically recognized as infected with *Trichophyton* gives positive reactions when tested against this organism.

It must be emphasized that we have been routinely testing during the past three years all our patients, irrespective of symptoms, with the McCammon *Trichophyton*. Approximately twelve positive skin reactors have been encountered in four hundred patients. Four of these twelve sensitive cases are included in this series of vasomotor rhinitis.

This contribution, which establishes molds as important etiologic factors in certain types of vasomotor rhinitis, makes possible specific desensitization. It is accordingly gratifying to note that relief from distressing symptoms has been accorded thereby; and thus, allergy becomes a worthy ally to clinical medicine. Six of the eight patients in our series have been under treatment for a long enough period of time to permit of a just evaluation of the newer therapeusis. A summary of the results of treatment follows:

GROUP I

CASE 1.—When last seen on November 3, 1930, this patient reports: "Getting along just fine—rare sneezing, occasional running of the nose. Stuffiness of the nose has gone." No reply to a follow-up letter has been received.

CASE 2.—Patient was last seen May 8, 1931. Under date of September 22, 1932, the mother of the young patient writes: "his entire condition has been one of steady improvement . . . . fits of sneezing have entirely disappeared except for the usual normal amount. . . . . Occasionally, a change in temperature will affect his nose but it does not last."

CASE 3.—This patient was last treated on June 1, 1931. During the course of treatment there was noted a marked and progressive improvement in the extreme stuffiness of nose which interfered with sleep.

CASE 4.—Date of last visit was September 3, 1931. Under date of Sephave had only one bad spell with my nose. My breathing is much freer tember 29, 1932, this patient reports: "I have gained twelve pounds, and and in all it has aided my health. . . . ."

GROUP II

CASE 1.—Course of treatment concluded September 24, 1930. His father, a physician, writes under date of August 30, 1932, "He has had no evidence of a return of his hay fever since the termination of treatment."

CASE 2.—This patient was under treatment from December 3, 1930, to March 20, 1931. A letter from the mother dated August 12, 1932, reads as follows: "he has improved fully 80 per cent."

SUMMARY

1. The clinical features of two groups of patients, each containing four in number and presenting certain types of vasomotor rhinitis, are described.

2. Cutaneous and subcutaneous tests indicate sensitiveness of the patients to molds.

3. Of the mold preparations used in testing, *Alternaria* and *Trichopyton* are the only two which have been determined to be the cause of symptoms.

4. *Alternaria* is commonly found in dust.

5. *Trichophyton* is a common parasite of the integument of man, and thus human contacts may provide allergenic material.

6. The gratifying results of specific desensitization with appropriate mold extracts are recorded.

7. The distinction between sensitiveness to molds and infection with molds is worthy of emphasis.

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(For discussion, see page 114.)

ASTHMA FROM THE LIFE INSURANCE STANDPOINT*

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I CONSIDER it a great privilege to have been invited to present to this body of clinicians, who are devoting so much of their thought and time to the broad field of allergic manifestations, the results of the joint experience of the life insurance companies with regard to asthma cases.

Our code calls for a report on asthma, not hay fever, but with the present knowledge we have of allergic states and reactions, we know that this is a misnomer, as we are dealing with a systemic condition and the bronchospasm is one of its distressing features. Hay fever and asthma belong to the same church though in different pews.

Prior to 1907 the medical and actuarial departments of life insurance companies worked independently the one of the other. The former were selecting the applicants according to clinical findings and the proper evaluation of these in accordance with the knowledge and experience of the medical staff.

The latter, who deal largely with the laws of probability, and averages, and compound interest, and who are held responsible for the premium rates and the dividend scale, were busy with a study of the death claims and comparing the actual to the expected mortality in various groups, according to basic mortality tables. Their report was so comprehensive and illuminating with regard to the actual mortality obtained among certain groups of impairments, irrespective of the satisfactory examination, that a joint committee of the Association of Life Insurance Medical Directors and the Actuarial Society was appointed to investigate together the experience of the companies with regard to various impairments. Since then, these two departments have been working together, and the relationship of the actuary to the medical director is practically the same as that of the pathologist to the clinician.

The first conjoined report, published in 1914, comprised 17,790 deaths, and in Table I is listed the trend regarding asthma cases. All these were considered as standard business. (See Table I.)

The second report was completed this year, and covered the issues from 1909 to 1927, inclusive. It comprised 1,100,000 entrants; the number of deaths were 41,000. The trend regarding asthma cases is listed in Table II. The results of this investigation were compiled by the number of policies and not by amounts insured.

The proper interpretation of mortality statistics, regarding reasonableness of results, likelihood of fluctuations, and whether the material is

*Read before the fall meeting of the Society for the Study of Asthma and Allied Conditions, New York City, December 10, 1932.

TABLE I

	ACTUAL DEATHS	EXPECTED DEATHS	RATIO
A. Existing at examination, or one attack within two years of application	56	46	120%
B. One attack between two and five years of application	42	40.33	104%
E. Two or more attacks, the last one within two years of application	131	105.4	124%
F. Two or more attacks, the last one between two and five years prior to application	45	34.92	129%
	274	227	121% ±5

The Medico-Actuarial Mortality Investigation from 1885 to 1908, inclusive, comprised 17,792 deaths.

The mortality is relatively higher at the older than at the younger ages at entry.

The death rate from pneumonia and other respiratory diseases was slightly higher than the normal, but practically normal from tuberculosis. There were 16 deaths from cardiac asthma and pulmonary emphysema—many times the normal.

homogeneous, representative, and complete, requires the knowledge of experienced actuaries—especially when the vast material, coming from so many companies whose methods and standards of selection are so different, has to be scrambled together. If the volume of data in any involved group is large enough for the average to have full play, they can plot a so-called "normal curve." For example, in Table I the ratio of the actual to the expected mortality was 121 per cent ±5 for the entire group. This means there is an even chance that the true mortality is within 5 points of

TABLE II

		EXPOSED TO RISK	ACTUAL DEATHS	EXPECTED DEATHS	RATIO
X-C	Standard	12,344	84	67.99	124 ± 9
	Substandard	3,842	42	19.21	219 ± 22
G-H	Standard	23,239	128	120.99	106 ± 6
	Substandard	16,453	196	83.09	236 ± 12
X-C, G-H	Standard	35,583	212	188.98	112 ± 6
	Substandard	20,295	238	102.30	233 ± 9

The Medical Impairment Study from 1909 to 1927, inclusive, comprised 41,000 deaths.

In Class X-C the death rate from organic disease of the heart was three and one-fourth times the normal. In Class G-H it was two and one-half times the normal from organic disease of the heart, one and three-fourths times the normal from tuberculosis of the lungs, two and one-fourth times the normal from influenza, and three and one-half times the normal from pneumonia.

In a representative section of the material there were 16 deaths from asthma (cardiac) and pulmonary emphysema against less than one expected death.

Out of 186 deaths in a sample of the data, five-sixths were in the class, "Asthma, moderate or not specified," the balance being evenly divided between severe asthma and hay fever.

X-C Found on examination, or one attack within five years of examination.
G-H Two or more attacks, the last within five years of examination.

121 per cent, and thus lies somewhere between 116 per cent and 126 per cent. Also, it is nearly certain that it is within 15 points (three times five) above or below 121 per cent, that is, between 106 per cent and 136 per cent. Here is where medical selection is brought into the picture to classify and subdivide the best from the worst in the group and to give them a proper evaluation. Dr. Edward J. Campbell and Dr. Bolt, of the New York Life Insurance Company, very kindly sent me the result of an investigation they made on their company's experience with asthma, in order to compare it with the recent medical impairment study report. They approached the study with the very common clinical opinion that the allergic bronchial asthma, while annoying and sometimes distressing to the patient, is rarely fatal—in fact, that such patients are full of "pep" and vigor, and are among the best and most successful of the citizens in any community. Further, that the type of asthma particularly prone to produce an unfavorable mortality was that of cardiac origin. Their investigation is listed in Table III.

TABLE III

NEW YORK LIFE EXPERIENCE, ISSUES 1909-1927, INCLUSIVE

		ACTUAL DEATHS	RATIO
Standard	148	(Class too small)	
Substandard	1425	111	270%

The cases were then divided into three groups clinically:

MILD	MODERATE	SEVERE
25%	25%	50%

An analysis was then made according to duration of the policies. While the severe group showed a slight increase in the number of early claims, yet there was a fairly even and parallel distribution from one to over ten years.

The two predominating causes of death were heart disease and pneumonia, and these were practically equal in number.

The company with which I am associated does not do any substandard business for medical impairments; and, although our experience has been favorable in the group, there were too few cases and too few deaths to draw any definite conclusions.

In order to place before you the practicable application of the problem, I have listed the ratings that the joint committee has suggested as a result of the investigation (Table IV).

You thus have an opportunity of seeing how far contrary they run to your conceived ideas or past experiences. I should call your attention to the fact that those listed as standard were superselected in every respect save for the impairment; whereas, the substandard business was average or slightly worse than average, and included other factors than merely the impairment.

TABLE IV. RATINGS

HAY FEVER, MILD, SEASONAL ONLY, NORMAL IN ALL OTHER RESPECTS AND ESPECIALLY IN REGARD TO NO UPPER RESPIRATORY INFECTIONS (SINUS TROUBLE AND OBSTRUCTIVE NARES)—STANDARD.

MILD ASTHMA ATTACKS IN THE PAST, NO ATTACK FOR THREE TO FOUR YEARS, NORMAL IN OTHER RESPECTS—STANDARD.

Last attack within two years:		
Mild	Occasional	+10 to +30
	Frequent	+25 to +50
Moderate	Occasional	+25 to +50
	Frequent	+50 to +100
Third year:		½ of above ratings
Fourth year and later:		0
Last attack within two years:		
Severe	Occasional	+50 to +100
	Frequent	+100 to risk not approved
Third year:		½ of above ratings
Fourth year:		⅓ of above ratings
Fifth year and later:		0

This impairment is more important at the older ages, over aged forty years. This is not shown in the medical impairment study, probably due to the strict selection.

DISCUSSION

Truism 1.—Although the mortality ratio may be less than or a little over 100 per cent, the causes of death indicate how the impairment is prejudicial to longevity. The two main causes of death in each of the investigations were found to be disease of the lungs or disease of the heart.

Truism 2.—The effect on longevity is not, as one would suppose, in direct ratio with the length of time that has elapsed or the severity of the acute and prominent manifestations of the disease. In fact, it may prove to be worse, due to a false sense of security on the part of the applicant in regard to the necessity of continuing the preventive measures instituted, and also to a relaxation in the medical selection. This was shown in the New York Life investigation, where it was found that those which appeared to be clinically mild showed proportionately as many early claims and as many claims in ten years as the clinically severe.

3.—The age of forty years in this, as in many other impairments, is the borderline. That is, those under forty years at time of entrance are better than those over forty years. It has been stated that four-fifths of all cardiac and circulatory deaths after forty-five years of age fall into the arteriosclerotic class.

4.—In allergic or bronchial asthma we have an organism whose pulmonary tissues and circulation are sensitized by protein substances of bacterial or plant or animal origin—in fact, a generalized toxicosis, acting over a long period of time, together with a mechanical obstruction to expiration due to the bronchial spasm. In consequence, we have ideal conditions for the production of capillary fibrosis and arteriosclerosis of the pulmonary circulation and the later development of chronic emphysema and disturbances of cardiac compensation.

5.—The work you are doing in the allergy clinics is health work and not bedside work. Therefore, your prognostic vista has to be much further than the usual two-to-five-years vista of the bedside clinician. The life insurance vista begins where the bedside vista ends.

If by this study you can gain some reassurance with regard to impressing your patients with the importance of continuing to be rechecked and following instructions, I know there will ensue a benefit to all concerned in maintaining the *mens sana in corpore sano.*

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SOME RHINOLOGIC ASPECTS OF ALLERGY*

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THE relationship of sinus disease and nasal pathology to bronchial asthma still awaits solution. There have been those who have claimed that asthma and vasomotor rhinitis are the result of nasal pathology and should be treated as such. There are others who insist that allergy is the only basis to be considered. Protagonists of both theories have amassed statistics in support of their claims, but we find these figures worthless for comparative analysis since they entail a variation out of all proportion to the number of cases studied. The incidence of sinus disease and gross nasal pathology in asthmatics has been reported as low as 14 per cent and as high as 90 per cent,[1 to 7] with other figures ranging all the way between. The incidence of sinus disease in asthmatic children has been reported as low as 6 per cent and as high as 100 per cent[1] (Tables I and II).

TABLE I

PERCENTAGE OF ASTHMATICS SHOWING SINUS DISEASE OR GROSS NASAL PATHOLOGY (REVIEW OF LITERATURE)

AUTHOR	REFERENCE NUMBER	DATE	NUMBER OF CASES	FINDINGS	PATHOLOGY PER CENT
Francis	1	1929	402	N.P.	14
Gottlieb	1	1925	117	S.D.	26
Lublinski	1		500	N.P.	29
Gill Cary	1	1930	110	S.D.	50
Adam	3	1900	640	N.P.	60
Dundas Grant	2	1913	107	N.P.	63
Tobey	2	1929	1000	N.P.	65
Schenck & Kern	4	1929	18	N.P.	67
Vaughan	10	1932	154	N.P.	71
Hansel	5	1925	400	S.D.*	75
Kern & Donnelly	6	1932	200	S.D.**	80
Smith	7	1929	***	S.D.	82
Matthews	2	1914	300	U.R.L.	90

*Lipiodol positive; **X-ray studies positive; ***Not stated.
S.D.—Sinus disease; N.P.—Gross nasal pathology; U.R.L.—Lesions of upper respiratory tract.

TABLE II

SINUSITIS IN ASTHMATIC CHILDREN

AUTHOR	REF. NO.	DATE	NO. CASES	FINDINGS	PER CENT
Bullen	1	1930	235	S.D.	6
Chobot	1	1930	100	S.D.	41
Lierle	1	1926	20	S.D.	100

I think, however, that we can agree with the majority of observers in stating that the incidence of gross nasal pathology or sinus disease is high

*Presented at the annual meeting of the Michigan State Medical Society, Kalamazoo, September 15, 1932.

in asthmatics. In my own series I find 71.2 per cent as showing evidence of past or present nasal pathology.[10] I do not know that this figure is any higher than it would be for a similar group of nonallergic individuals. As a matter of fact Kern and Donnelly[6] found in Philadelphia in a study of 50 nonallergic controls that 72 per cent suffered from sinus disease. This figure was almost as great as their own recorded incidence of sinus disease in bronchial asthma, namely 80.5 per cent.

When we study the reports of results of treatment, we again observe figures that can scarcely be reconciled (Tables III and IV). The reported

TABLE III

RESULTS OF RHINOLOGIC TREATMENT IN ASTHMA

AUTHOR	REF. NO.	NO. CASES	"CURE"	GOOD	BOTH
Kahn	2	N.S.	0 %	0 %	0 %
Heatley & Crowe	2	62	1.5%	0 %	1.5 %
Rackemann	2	Review of Literature	5 %	10.20%	10.20%
Bray	1	Review of Literature	14 %	—	—
Stout	2	Polyps	11 %	—	—
		Sinuses	22 %	—	—
Leopold & Fetterolf	2	24	20 %	—	—
Tod	1	202	10 %	49 %	59 %
Lierle	2	21	10 %	81 %	91 %
Smith	7	N.S.	74 %	26 %	100 %

N.S.—Not stated.

TABLE IV

RESULTS OF ALLERGIC TREATMENT IN ASTHMA

AUTHOR	REF. NO.	NO. CASES	"CURE"	GOOD	BOTH
Walzer	9	Review of Literature	20-30 %	25-35 %	45-65%
Rackemann	2	425 Extrinsics	25 %	57 %	82%
		499 Intrinsics	18 %	52 %	70%
Vaughan	10	99 Extrinsics			68%
		55 Intrinsics			27%
Clarke	2		20 %	41.7%	61%
Menaugh	2	300	28.3%	27.7%	56%
Rowe	2	110	68.3%	22.7%	91%
Alexander & Zeek	11	69 Uncomplicated			90%
		123 Complicated			24%

cures of asthma following rhinologic surgery range from 0 per cent to 54 per cent while reports of satisfactory relief including cure and near cure range from 0 to 100 per cent. Those who treat asthma as an allergic condition report cures anywhere from 20 to 68 per cent and good results from 24 to 91 per cent.

Obviously therefore figures are available to substantiate whatever stand one may choose to take. These series of results are not susceptible to direct comparison for several reasons. As a rule there has been no attempt to classify the patients, the feeling evidently being that the diag-

nosis of asthma was sufficient classification. But there are many forms of asthma, the two great groups being the extrinsic and the intrinsic; there are many types of exciting causes; and there are many kinds of contributory local pathology which play a part in the prognosis. Conclusions have usually been drawn from studies of groups too small to warrant generalization. Too often only one aspect of the disease, either the rhinologic or the allergic was considered. Surgical methods have varied widely. Finally, one suspects that the follow-up of end-results was frequently not carried over a sufficiently long period. Certainly, those who have had any wide experience with asthma know that, provided enough time elapses, a gradually increasing number of patients will again manifest symptoms.

COLLABORATIVE STUDIES

We may anticipate much more of value from the more recent method of investigation in which both the allergist and the rhinologist collaborate, realizing that allergic factors and nonallergic factors may interact in the production of symptoms. The progressive allergist today does not hesitate to call upon the otolaryngologist whenever indications arise, and increasing numbers of nose and throat men are recognizing an allergic intranasal picture in the presence of which they call upon the services of the allergist. While several such groups have made noteworthy contributions, I should mention particularly the work of Rackemann and Tobey in Boston, of Kern, Schenck and Donnelly in Philadelphia and of Alexander and Hansel in St. Louis.

One should first recognize that not all asthmatics are the same. There are two general subdivisions, the extrinsic and the intrinsic.[2] Any compilation of results that does not classify the asthmatic as extrinsic or intrinsic or by some equivalent nomenclature, is inconclusive. The extrinsic case is a typically allergic asthmatic. The exciting cause is contact with some specific allergen to which the individual is sensitive and with which he comes into contact through the skin or the respiratory or

TABLE V

DISTRIBUTION OF 154 ASTHMA CASES WITH RESULTS OF TREATMENT

RESULTS	EXTRINSIC 99 CASES (64%)	INTRINSIC 55 CASES (36 %)
Excellent	38.4%	10.9%
Good	29.3	16.4
Fair	15.1	10.9
Poor	15.1	52.7
Bad	2.1	9.1
Excellent		
Good	67.7%	27.3%
Excellent		
Good		
Fair	82.8%	38.2%

digestive tracts, and from some source outside the body. In the pure intrinsic case, no such external excitant can be discovered. Intrinsic asthma is sometimes spoken of as infectious asthma but infection is probably not the only factor at work in the intrinsic case. Rackemann found 46 per cent of his asthma series intrinsic, Harkavy and Maisel[16] found 47 per cent of theirs nonsensitive, and I have found 36 per cent of mine to be intrinsic (Table V).

In hay fever, provided desensitization therapy is properly applied, results from allergic methods far excel those from any other form of treatment. No other method will ensure better than 75 per cent relief to over 80 per cent of patients and 90 to 100 per cent relief to two-thirds. Kern and Donnelly[6] have shown that local nasal pathology, even actual sinus infection does not interfere with good results in hay fever. Hay fever patients with untreated sinus pathology did as well as those without sinus involvement.

Allergic therapy produces best results in extrinsic asthma and should be the method of choice. As in hay fever, good results are often obtained irrespective of local nasal pathology. Satisfactory relief in my experience was obtained in 68 per cent.[10] This is about the usual conclusion; although Rackemann in a series of over 425 extrinsics reports better results, 82 per cent, while Alexander and Zeek[11] report 90 per cent satisfactory relief in their uncomplicated cases. The results with intrinsics following allergic therapy are quite different. While Rackemann reports 70 per cent with adequate relief, most figures are lower, my own being 27 per cent and Alexander's 24 per cent.

There is the residual group of extrinsics, probably about 25 per cent, and the entire group of intrinsics, in whom relief may sometimes be secured through rhinologic treatment. This gives us roughly about half of the chronic asthmatics in whom nasal or other local nonspecific pathology may require adjustment.

SURVEY OF RHINOLOGIC FACTORS

The following survey of the rhinologic factors is based on a series of 154 asthmatics selected out of a total series of 300. The only requirements in the selection were, adequate available information from rhinologic study along with the allergic study, and adequate follow-up over a period sufficiently long to determine results (Table V).

Of the total series 36 per cent were intrinsic asthmatics and 64 per cent were extrinsic. Results were classified as excellent, good, fair, poor and bad. The bad result cases included those who for one reason or another became worse during their period of supervision. Including the excellent and good cases, 27.3 per cent of the intrinsics and 67.7 per cent of the extrinsics obtained adequate relief from allergic methods only. If we were also to include the fair result cases, these figures would be 38.2 per cent for intrinsics and 82.8 per cent for extrinsics (Table V). These figures ap-

proach more nearly those reported by Rackemann, but in order to avoid too optimistic a tendency in the remainder of this discussion we shall consider only the first two classes as having obtained satisfactory results. The basic figures for comparison are roughly 27 per cent for intrinsic asthma and 68 per cent for extrinsic.

Of the entire series 33.8 per cent had previously been subjected without relief to nasal surgery. Thirty-two of the 47 were extrinsic cases, cases which should not have been treated surgically without preliminary allergic study (Table VI).

TABLE VI

ANTECEDENT NASAL SURGERY IN 139 CASES

Extrinsic (95 cases)	32 cases
Intrinsic (44 cases)	15 cases
Total	47 cases or 33.8%

Of 95 extrinsics 32 had been subjected to nasal surgery. Of these 32, 15, or 47.9 per cent, reported good results from allergic therapy. Sixty-three had had no precedent nasal surgery, and of these 47, or 74.6 per cent, reported good results from allergic treatment. In the extrinsic group (Table VII) the results were much better among those who had not had

TABLE VII

EFFECT OF NASAL SURGERY ON RESULTS OF ALLERGIC TREATMENT

	EXTRINSIC	INTRINSIC
No. cases	95	44
No. who had had surgery	32	15
No. of latter with good results	15	2
Per cent with good results	47.9	13.3
No. who had not had surgery	63	29
No. of latter with good results	47	11
Per cent with good results	74.6	38.0

previous nasal surgery. One might argue that the poorer results in the operative cases were due to the presence of local nasal pathology, or one could argue equally well that the figures indicate that in extrinsic allergy nasal pathology is better left alone, certainly until allergic therapy has been given a trial. In favor of the latter is the observation that 27 or nearly three-fifths of those who had had no surgery and reported good results, did actually have nasal pathology, and the good results were obtained in spite of the fact that this was not treated.

I believe that there is some truth in both arguments, since the same differences were observed in the intrinsic cases. Of 44 intrinsic cases 15 had had antecedent nasal surgery, and of these only 13.3 per cent reported

good results. Of the 29 who had not been subjected to surgical treatment, 38 per cent reported good results.

One conclusion, however, stands out definitely, that relief can often be obtained by allergic methods alone, even in the presence of nasal pathology. At the same time I am firmly convinced that nasal pathology is often a deterrent to adequate relief both in the intrinsics and in some of the extrinsics. Taking both groups together, 40 showed evidence on physical examination of nasal pathology and had had previous nasal surgery (Table VIII). Of these only 35 per cent reported good results. Fifty-

TABLE VIII

NASAL PATHOLOGY AS A FACTOR IN RECOVERY—132 CASES

	NO. CASES	PER CENT OF GROUP	NO. RELIEVED ALLERGICALLY	GOOD RESULTS PER CENT
1. Nasal pathology treated	40	30.3	14	35.0
2. Nasal pathology not treated	54	40.9	32	59.3
3. No nasal pathology	38	28.8	26	68.4
4. Nasal pathology (1 and 2)	94	71.2		
5. 1 and 2 subjected to previous surgery			42.5%	
6. Showing nasal pathology but not operated on			58.7%	

four had not had previous surgery but did show evidence of nasal pathology on physical examination, and of these 59.3 per cent reported good results. But best results were obtained in the 38 who showed no evidence of nasal pathology and gave no history of nasal treatment and who reported 68.4 per cent with satisfactory results. These 38 are obviously strictly allergic cases and could expect no relief from any form of nasal treatment. They represent 28.8 per cent of the entire series.

Considering the matter of turbinate pathology alone, among the extrinsic cases with normal turbinates, 78.5 per cent were relieved. Among the extrinsics with turbinate pathology 60.6 per cent were relieved. Among the intrinsics without turbinate pathology 43.8 per cent were relieved, and among the intrinsics with turbinate pathology only 26.9 per cent were relieved (Table IX).

Whether the turbinate pathology is cause or result, the fact is that persons with turbinate pathology (other factors not considered) do not do so well. This is true even of the extrinsic cases.

Summarizing this portion of our discussion, 71.2 per cent of the series showed evidence of gross nasal pathology either in the past or at the time of first examination. Of those showing nasal pathology, 42.5 per cent had been subjected to some form of surgery. Results were decidedly better among those who had had no previous surgery, even though 59 per cent of these had clinical nasal pathology, which was not treated. The ethmoid region has long been considered an asthmogenic area in certain cases, and

TABLE IX

EFFECT OF TURBINATE PATHOLOGY

TYPE OF PATHOLOGY	PER CENT WITH GOOD RESULTS	
	EXTRINSICS	INTRINSICS
No pathology	78.5	43.8
Edematous Contact Polyps	64.1	23.5
Edematous Contact Polyps Ethmoiditis	60.6	26.9

we find evidence that, other factors not considered, patients with turbinate pathology do not do so well as those without.

The inference which I would draw from these observations is that from the rhinologist's point of view the early treatment of an asthmatic with local nasal pathology should be conservative, nonsurgical. If these measures do not achieve adequate relief, a complete allergic study should then be made and allergic therapy should be carried out long enough to obtain as good results as may be obtained by this method. Following this, if relief is still inadequate, more radical nasal surgery may be undertaken as indicated. There is no gainsaying that sinus surgery occasionally produces spectacularly good results in asthma. Unfortunately it is usually not permanent.

For example, Schenck and Kern[12] observed that following the Caldwell-Luc operation 83 per cent experienced complete relief. In one-third of these the relief continued for from three to seven and one-half months. In slightly over a half the relief was temporary, lasting from a few weeks to two years, 17 per cent had no relief at all. Even this operation does not necessarily permanently cure the antrum infection. They found in patients who had had previous Caldwell-Luc operations that the antra contained dense, fibrous tissue with loculated collections of pus and polypoid tissue.

THERAPEUTIC PROGRAM

It becomes apparent from the preceding discussion that the attitude of the allergist toward local nasal therapy is one of conservatism. Obstructing polyps should be removed particularly if there is not a speedy response to allergic therapy. Submucous resection is not indicated unless for the relief of contact and definite obstruction. Turbinectomy is to be avoided since following this operation cooler rawer air enters the bronchial tree and this sometimes produces exacerbations of the asthma. Since asthma is sometimes relieved by allergic methods in

spite of local nasal pathology, these should be tried first. On the other hand, if in spite of adequate trial with allergic therapy and conservative nasal therapy the condition persists, and if there is evidence of sinus pathology, more radical procedures should be inaugurated. In such cases the operation of choice should be that which offers greatest promise of relieving the sinus condition, quite irrespective of the presence or absence of an allergic state. Nasal surgery will be indicated more often in the intrinsic type of asthma than in the extrinsic. This represents 35 to 45 per cent of chronic asthmatics.

NASAL PICTURE

There is a rather characteristic nasal picture of allergy. The outstanding feature is a boggy, edematous mucosa involving more especially the middle turbinate, often with polypoid degeneration and with a mucoid discharge which may be semipurulent. While the surface may be reddened and rough-looking it is more often pale, shiny, pink, sometimes even pearly. The picture is usually bilateral, in contrast to primary suppurative conditions which are more often unilateral. X-ray examination of the sinuses, especially with lipiodol will often show thickened membranes and polypoid hyperplasia. Proetz, using lipiodol, has observed sudden edema of the antral mucosa during an allergic attack comparable to the allergic reaction in the bronchi and in the skin. The local clinical picture and pathologic findings have been very ably described by Hansel.[13]

Eosinophils are often observed in the nasal secretion. Eyermann[14] observed eosinophils in 72 per cent of allergic secretions and in 9 per cent of nonallergic secretions. Cohen and Rudolph[15] conclude that a nasal secretion smear showing 10 per cent or more eosinophils is diagnostic of allergy.

SUMMARY

By way of summary I would say that in chronic bronchial asthma local nasal surgery may be indicated especially in the intrinsic cases and in those extrinsic cases who have failed to respond to allergic therapy. This represents upwards of one-half of the total.

Local nasal surgery is not indicated in cases of extrinsic asthma without preliminary allergic study. In spite of this I find that two-thirds of my series that had previously been operated upon were extrinsic cases. Surgery did not relieve them, and they should not have been operated upon.

From the allergic point of view best results are obtained in the absence of local nasal pathology, especially turbinate pathology. But good results are often obtained allergically in the presence of nasal pathology even though the latter is not treated locally. Three-fifths of my good result cases showed definite nasal pathology, for which no local treatment was given, and yet the results were good.

CONCLUSIONS

When the local picture suggests allergy, further confirmation can usually be obtained by questioning the patient concerning other allergic manifestations and concerning a family history of allergy. It is not sufficient to inquire merely for personal or family history of asthma, hay fever or urticaria. Allergy may also be manifested as periodic headaches, eczema, colitis, food upsets or disagreements, sneezing barrages, intolerance of dust, angioneurotic edema, drug idiosyncrasy, etc. The finding of positive cutaneous reactions to specific allergens further establishes the diagnosis.

All that has been said concerning asthma applies equally to vasomotor rhinitis. In both conditions best results will be obtained from close cooperation between the rhinologist and the allergist. Even so, we shall find that there is a certain residual percentage which will not respond even to these combined efforts and which impress upon us a realization that, in spite of all of the advances that have recently been made in our understanding of the allergic diseases, we are still in large measure ignorant of the underlying pathologic process which makes one person appear allergic and another nonallergic.

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URINARY PROTEOSES IN BRONCHIAL ASTHMA —A CLINICAL STUDY*

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IN SPITE of the progress in the field of allergy during the past decade the treatment of bronchial asthma still presents many problems difficult to solve. A great number of chronic asthmatics are still unable to get any relief because the present methods of study fail to establish the etiologic factors which are so essential for success in treatment.

During the last two years we have encountered a number of such patients in our clinic. They were all definitely asthmatic. Some gave positive skin tests to many inhalants and ingestants; others reacted to a very few substances; a few reacted to bacterial toxins. Treatment based on specific findings; nonspecific methods; elimination diets; surgery of the paranasal sinuses, and what not, failed to give any relief worth mentioning.

Recently the work of Oriel[1] and his coworkers of Guy's Hospital, London, attracted our attention. The above investigators, while studying the biochemistry of allergy, were able to extract from the urine of such patients a substance which is present in large quantities during the allergic state, and which they named "proteose." Later on, Oriel[2] stated that they called it proteose for the sake of brevity, although it is not a true proteose. This substance, according to them, "contains nitrogen, and is apparently of a protein nature containing a considerable carbohydrate group, and is chemically similar to the specific part of the tubercle bacillus isolated by Dudley and Laidlaw, and of the pneumococcus isolated by Dochez and Avery." This substance is supposed to give a positive skin reaction which is specific for each patient and is very useful as a therapeutic agent for desensitization. They were able to obtain this substance in the urine of patients afflicted with asthma, hay fever, many skin conditions belonging to the so-called allergic group; rheumatoid arthritis, influenza, tuberculosis and serum sickness. In their subsequent investigations they were able to repeat and thus confirm their first observations, reporting many successful results in patients previously treated by many other methods with failure. It was also favorably reported on by the Asthma Research Council of King's College, London.[3]

Ward and Whitehead[4] were favorably impressed with their results on repeating the work of the above investigators. They obtained some proteoses even in the urine of normal individuals; however, they were unable to obtain positive skin reactions in such individuals, whereas they were always able to obtain positive skin tests with the proteoses from their hyper-

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sensitive cases. They, therefore, concluded that there must be a change in the urinary proteose of the allergic, that an additional substance is excreted in close association with it. They quote Gurd, who thinks that the reaction may be due to a secondary antigen resulting from the action of the primary antigen on the tissues, especially the liver. Oriel and Barber share the same view. Ward and Whitehead[5] found no relation between the quantity of the proteose obtained from the urine and the skin reaction. They also report an increase in the total leucocytes and in the eosinophiles following treatment with proteoses. To quote their therapeutic results: "*encouraging* results have been obtained in asthma, subdeltoid bursitis, urticaria, and hay fever." Also "desensitization with proteose *apparently* resulted in improvement in six out of nine cases of asthma studied." Favorable comments are also made by Rackemann[6] and Douthwaite.[7] It was therefore with great interest and hope that we set out to try the above method.

In the study of the first three of our cases we were unable to obtain anything from the urine which would give a positive skin test. We, therefore, communicated with Oriel who was kind enough to inform us of some modifications of his original method which he thought would give us better results. Ever since November, 1931, we have employed this modified method, which is as follows:

About 400 c.c. of urine are collected from a patient having active symptoms—in our cases it had to be a paroxysmal attack of asthma. The urine is preserved during that period with 5 c.c. of chloroform. The specimen is rendered acid to Congo red with sulphuric acid and shaken in a separatory funnel with 10 c.c. of ether. After the two layers are separated, the lower layer is run off and discarded and the upper ethereal layer treated with an equal volume of alcohol and the resultant white precipitate allowed to settle. The latter precipitate is then collected by centrifuging in a sterile centrifuge tube. Afterwards it is again suspended in a small quantity of sterile distilled water and recentrifuged. To the precipitate so obtained, which presumably contains the active proteose constituents, is added a small quantity of sodium hydroxide, thus dissolving any contained proteose. This solution is diluted with a buffered saline solution and represents what Oriel considers a standard 1:100 solution. In a few instances we passed the final solution through a Berkefeld filter. All solutions were kept in sterile vaccine bottles and dilutions were made from these. Our dilutions were 1:10, 1:100, and 1:1000 of the standard.

We selected eight patients for clinical study. All of them were definitely asthmatics, as determined by the history, positive skin tests and invariable relief of their attacks by adrenalin chloride. In a few of them we demonstrated reagins by the method of Prausnitz and Küstner. Their ages varied from thirty-two to forty-seven years, and the duration of asthma from five to twenty years. They were three females and five males.

The technic was religiously observed. No urine was collected during a remission. Sufficient quantities were collected during attacks and precautions taken to prevent deterioration. This was personally attended to.

We attempted to establish the following: (1) the presence of a proteose; (2) the specificity of each proteose as determined by skin test; (3) the effect of the proteose on the skin of other asthmatics; (4) results of treatment.

Our tests were made by the intradermal method and not more than 0.01 to 0.02 c.c. used in order to prevent nonspecific reactions. Satisfied that we had obtained the so-called proteose, we proceeded with our observations.

CASE 1.—B. C., aged forty years, had asthma of five years' duration. Marked skin reactions to local home factors, viz., dust and feathers, were obtained. Reactions to his own proteoses were very slight with similar reactions to proteoses of the other patients. Treatment was instituted by administering 0.1 c.c. of a 1:100 dilution subcutaneously twice weekly. The dosage was doubled with each subsequent visit until full strength dilution was reached. After two months of treatment no improvement whatsoever was observed and treatment was discontinued.

CASE 2.—S. A., aged thirty-two years. Asthma persisted since the age of fifteen years. Marked skin reactions to house dust, feathers, animal dander, especially horse epithelium, and ragweed were obtained. For the last three years symptoms have been aggravated during late August and September.

Skin tests with autogenous proteose yielded no reaction even with the full strength, although there was considerable local itching which was obtained even by the lower dilutions. Similar results were obtained with the proteoses from other patients. In spite of this, treatment with the patient's own proteoses was continued for a period of three months; at no time was there any evidence of constitutional reaction, nor was there any evidence of relief beyond the occasional period of remission incident to asthmatics.

CASE 3.—I. K., female, aged forty-four years. Asthma of sixteen years' duration was present. The patient has also been subject to urticaria. Skin tests were positive to a number of foods and bacterial proteins. Reaction to own proteoses and those of other patients was negative. Treatment was instituted with the full strength proteoses, with the result that the patient developed a severe urticaria. Similar results followed when 1:10 and 1:100 dilutions were used. Her asthma, however, was neither aggravated nor improved. She became very uncooperative and refused further treatments and tests. Treatment was continued for a period of four weeks.

CASE 4.—M. K. had asthma of many years' duration with periods of remission. She also has gastrointestinal allergy. She reacted by skin test

to most of the foods and many inhalants. A very slight reaction to her own proteoses occurred. Treatment was not carried out because the patient left the hospital.

CASE 5.—A. P., aged forty-one years, had asthma of three years' duration. Numerous skin reactions were recorded from moderate to marked to many foods and inhalants. A slight reaction to autogenous proteoses and similar reaction to those of other patients occurred. Treatment for a period of three months failed to give any relief, nor did it aggravate the symptoms.

CASE 6.—J. B., aged forty-one years, had asthma of twenty years' duration. Symptoms were worse from May to October. Skin tests gave a slight reaction to house dust, birch, oak, plantain, timothy and ragweed. Marked relief was obtained last year with pollen treatment during the summer months. Proteoses were collected in December, 1931. Skin tests to these were negative. Treatment with full strength proteose for a period of four weeks did not influence his condition one way or another.

CASES 7 and 8 are merely repetitions of the first three cases; hence no detailed reports are necessary.

DISCUSSION

We believe we obtained something from the urine which corresponds to the urinary proteoses. We were unable to obtain in skin testing our patients with this, anything beyond a slight reaction, even to the highest strength dilution, while marked reactions to other allergens were obtained. We noted similar slight reactions on cross testing with proteoses from other patients. No relief in any of our patients was obtained by treating with proteose.

Other investigators have similarly been unable to report favorably on the work of Oriel. Freeman[8] conducted a series of intradermal tests using both the injection method as employed by Oriel, and his own "prick" method on the three following groups of individuals: hay fever subjects, normal nonallergic subjects, and allergic but non hay fever subjects. He employed as test materials: (1) proteose in part supplied him by Oriel and in part prepared by himself, isolated from hay fever patients during active symptoms; (2) proteose isolated from the urine of non hay fever patients—"nonspecific" proteose; (3) saline solution, and (4) a pollen extract with saline as a control.

In all Freeman performed about 500 tests and noted that whereas he obtained positive reactions in hay fever patients and negative reactions in the other two groups with the pollen extract he noted no difference among the three groups with regard to the so-called "specific" proteose and "nonspecific" proteose. He refers in this paper to unpublished results of Dr. George Bray who has employed "specific" proteose in treatment of such cases without obtaining the positive results described by

Oriel. This paper by Freeman is an elaboration of previous work and correspondence by him in which he finds himself unable to repeat and confirm the original work of Oriel in this regard.

Doubtful results were obtained by Lyon, Percival and C. P. Stewart[9] in a series of cases with serum urticaria.

We are not prepared to explain the cause of the itching and the urticaria, nor is this crucial to our discussion. However, it is interesting that Ward and Whitehead met occasional focal reactions, but no itching in their cases.

The presence of leucocytosis and eosinophilia reported by Ward and Whitehead is also of interest. It is well known that eosinophilia in asthma is present only during and immediately after the paroxysmal attack. One is justified in concluding that the proteoses set up a leucocytic reaction, stimulating the eosinophilic group chiefly, and that it has no specific allergic effect.

When one deals with such a disease as asthma, where remissions are so frequent, one cannot jump to conclusions as to the efficacy of a certain therapeutic measure, unless evidence is beyond doubt.

CONCLUSIONS

1. There is a substance in the urine of asthmatics reported by Oriel as "proteose."

2. While we isolated this urinary substance we were unable to obtain any marked reaction to it on skin testing. The reaction obtained was not specificity, since similar reactions were elicited on cross testing with the urinary proteoses from other patients.

Urinary proteoses in our hands failed to justify its claim as a therapeutic measure let alone a specific one.

We wish to express our thanks to Drs. George I. Blumstein and Isadore Katz, junior members of the Asthma Clinic, for their assistance in this work.

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ALLERGIC PRURITUS—NEUROTIC EXCORIATIONS

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A NUMBER of skin diseases are considered more or less generally of allergic origin; such as, urticaria, angioneurotic edema, eczema and certain forms of prurigo (Rackemann,[1] Rowe,[2] M. B. Sulzberger, et al.[3]). It is about the same group of skin diseases that are regarded by others as psychogenic (Flaudrin,[4] C. Bunneman,[5] Reich,[6] Sack[7]). The frequent qualification of both statements with "may" and "in certain cases" eliminates some contradiction.

Investigations concerning pruritus, that is, itching without visible skin eruptions, due to allergy, are scarce. Rowe mentions itching about the nasal and oral cavities in asthma, and also pruritus ani and vulvae due to food sensitiveness. It is clear from the report of his cases in the latter group that they manifested actual skin eruptions. Balyeat[8] described cases of localized pruritus of the neck and chest in asthma, and Wynne[9] two cases of senile pruritus due to sensitiveness to wheat. It is understood that in discussing pruritus due to allergic origin, other causes (icterus, leucemia, etc.) are excluded. The same applies, of course, to cases of pruritus attributed to psychogenic factors (Strandberg[10]). It is generally known that the trauma of scratching can produce secondary skin infections, and even the pruriginous eruptions are considered secondary manifestations by many. Neurotic excoriations are to be sharply differentiated from all above mentioned skin conditions. They are self-inflicted skin lesions of lesser or greater gravity (burns, wounds, etc.) as to the origin of which the patients usually plead ignorance. They may be manifestations of hysteria or of a psychosis, usually schizophrenia, relating them to various delusions. They should not be confused with malingering.

The case to be reported relates to practically all problems that have been touched upon. Before proceeding to the case itself, two more or less generally known facts should be mentioned in reference to the question of allergic itching: (1) Some of the manifest pruriginous eruptions are preceded by itching for a long time, sometimes years. (2) Attacks of urticaria often alternate with those of itching without manifest eruptions.

CASE REPORT

A. T., a very intelligent female (college graduate and writer), thirty-six years old, came for advice about three ulcers on her face, one on the ridge of the nose, one on the left cheek, each of the size of a quarter, and a small ulcer on the right eyelid at the palpebral ridge, and also some ulcers on the breasts and on the abdomen. Questioning elicited the story

that the patient had been having various lesions of similar nature for the past twenty years during which time she consulted some fifty physicians, neuropsychiatrists, psychoanalysts, dermatologists, otolaryngologists, etc. She stated that she produced the ulcers herself with her nails, with needles and scissors. On being asked why she did that, she answered that she was having cysts under her skin produced by ingrowing hairs, a sort of subcutaneous beard which produced a certain sensation from which there was no relief unless those cysts and hairs were removed. She had the same sensations within her nose, supposedly due to the same cause, and she therefore had to perform similar "operations" within her nose. She could not be convinced of the anatomic impossibility of her explanation because she considered her "sensation" and the relief subsequent to her "operations" a proof that it was correct. In fact she produced as objective evidence an envelope filled with pieces of hair that she had allegedly removed from the "cysts" in the course of her "operations."

The patient's mental affliction seemed rather grave. In the course of years she had entirely destroyed the tip of her nose including the cartilage and had just recently undergone a plastic operation. The last ulcer she produced was in the center of the new skin graft. Her refusal to see the impossibility of her "explanations" and her objective proofs (collection of hair from the scalp and threads of cotton) all seemed aggravating circumstances. Yet the patient's whole attitude during the examination, her good contact, the lack of any delusions (after all, in her explanations she used half-sensible ideas), seemed to indicate that one was dealing with not a psychotic but a psychoneurotic state. It was also observed in the next few interviews that the patient, aside from fingering spots, would also scratch her face. On being asked why she scratched she said that it itched; and why she had not mentioned that before—that she had got tired of talking about it because nobody had paid any attention to it in the past ten years. This answer made a thorough survey of the patient's other unmentioned symptoms imperative, which survey on the other hand furnished a key to the patient's difficulties and led finally to an almost complete cure.

Allergic history and findings: (1) The patient's father suffered from generalized pruritus and chronic bronchitis. Her brother is suffering from chronic upper respiratory catarrh. Neither was seen by the examiner.

(2) The patient suffered from infancy (beginning about the sixth to ninth month, according to her mother's statement) from repeated attacks of "colds," conjunctival irritation and bronchitis. (Beginning of mixed diet?) The patient's description of her "colds" leaves no doubt of their being attacks of vasomotor rhinitis. The attacks of bronchitis stopped at the age of twenty-six years (ten years ago) following the administration of an "influenza vaccine."

(3) In her childhood, as far back as she can remember, the patient suffered from itching which she is inclined to attribute to the woolen underwear she was compelled to wear. She is not sure whether she had it in summer also. This itching stopped, she thinks, about the age of ten years. It is impossible to decide whether this itching was caused by the texture of the wool or by its chemistry (allergy). During the same period and practically up to date, she has been suffering from pruritus vulvae, though in a mitigated form after the age of ten years.

(4) Between the ages of seven and eleven years, the patient had repeated attacks of urticaria.

(5) Between the ages of twenty and twenty-four years, she suffered repeated attacks of angioneurotic edema which was localized on the upper and lower lips.

(6) Beginning at the age of fifteen years, the patient (for the last twenty years) has suffered from the peculiar sensations in her face and also to a lesser extent, her torso, that compel her to dig into her skin and remove whatever is causing that sensation. This sensation is difficult to describe. It is a feeling of "irritation," "swelling," "congestion," "crawling."

(7) The patient is not able to state definitely when her itching recurred. She is inclined to think it was about ten years ago. She is not sure whether it followed the administration of the "influenza vaccine." It is a generalized itch, very mild on the extremities, more marked on the torso, and fairly intense on the face, especially along the region of the lower jaw. The itching of the scalp does not quite go parallel with it. On close questioning the patient admitted that the itching itself was not accompanied by any skin eruption. This was confirmed later, when she stopped producing skin lesions.

(8) For the past fifteen years the patient has been having repeated eruptions of lichen simplex chronicus localized in the bend of the right elbow.

The allergic symptoms at the time of the first consultation were: (a) vasomotor rhinitis (clear watery discharge from the nose, without mucus, accompanied by congestion of the conjunctivae); (b) pruritus, as described above; (c) the peculiar "sensations" as described above (the allergic nature of this will be discussed later; it undoubtedly had a psychogenic component also and an irritative element secondary to the scratching); (d) lichen simplex (allergic nature doubtful).

The skin tests (intradermal) showed the following mild positives (2-plus) to foods: pork (with itching and erythema!), lima beans, corn, carp, cabbage, herring, brussels sprouts. A therapeutic test showed that the vasomotor rhinitis was caused by pork (bacon, ham) and by vegetables belonging to the cabbage family. Their omission from the patient's dietary made her free from the respective symptoms. Their in-

gestion regularly produced them, as did their intradermal inoculation. The peculiar sensations also seemed to vanish largely with the omission of pork and cabbage. Not, however, the pruritus. It was only after a trial with Rowe's[11] elimination diets that the patient became free from itching (on diet No. iii). Additions to that diet proved lamb, chicken, salmon, tuna fish and corn, the chief offending agents; whereas cod, shrimp and carrots were mildly productive of itching. It is obvious from comparison of the results of the skin tests and of the use of the elimination diets, that most of the foods productive of itching gave negative skin tests.

The emphasis in this communication is placed on the somatic (allergic) aspects of the case. This should not be interpreted in the sense that the psychogenic factors were not of equal importance in producing the main symptoms, the neurotic excoriations. The somatic findings chiefly explain why the patient's neurotic tendencies took this particular form of expression, the production of sores on the skin. The interrelation between the somatic and psychic in this case is actually more complicated. There are many interesting and important findings relating to this problem, in this case, which together with a detailed report of the psychopathologic findings, will be reported elsewhere. Suffice it to say here that the case is one of psychoneurosis, mainly of the hysterical type. The failure for twenty years in the past to recognize and to treat the somatic nucleus, led to a failure of all psychotherapy. This again does not mean that the patient was cured the minute she was given the explanation and the advice concerning her allergic manifestations. On the contrary, she still kept producing her sores. It took six months of psychotherapy, after the discovery of the allergic factor, gradually to wean the patient from her "addiction." In fact one task of the psychotherapy was to make the patient cooperate in the allergic investigation and treatment. The patient still has a mild itch occasionally (the multiple sensitiveness makes it difficult for her to avoid all offending foods), and she is still aware of some impulse to meddle with her skin, but she does not do herself any damage. For practical purposes she is cured. She also underwent three plastic operations on her nose (performed by Dr. Gustave Aufricht), in the course of the allergic and psychic treatment.

SUMMARY

1. Pruritus and other subjective skin complaints may be the manifestations of allergic sensitiveness.

2. These skin symptoms (together with vasomotor rhinitis), in the presence of other psychogenic determinants, may lead to a grave psychoneurotic manifestation: neurotic excoriations. A case is reported, with such a condition of twenty years' standing, that was cured by therapeutic measures directed at both the somatic and the psychic factors.

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INTOLERANCE TO WHITFIELD'S OINTMENT AS A CAUSE OF FAILURE IN THE TREATMENT OF EPIDERMOPHYTOSIS

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THAT epidermophytosis is at times an extremely rebellious disease to treat has become increasingly apparent during recent years. Failure to cure may be due to any one of several reasons:

1. Erroneous diagnosis. Nonparasitic eczema may involve the feet or toes as well as any other portion of the body and may be localized there exclusively. A suspected diagnosis of tinea should be confirmed by a microscopic examination of scrapings, and in case this is negative, by cultures on Sabourraud's medium.

2. Improper medication. A cure is not to be anticipated unless the treatment possesses active fungicidal properties. Many proprietary remedies which are widely advertised are hopelessly inadequate.

3. Insufficient treatment. It cannot be too strongly emphasized that the treatment must be continued until the lesion is normal, both clinically and microscopically. A patient should not be dismissed from observation until microscopic examination of scales fails to reveal any fungi.

4. Reinfection from shoes, floor, etc.[1] Inasmuch as fungi are extremely resistant to drying and to ordinary methods of sterilizing, the patient's shoes, bedroom and bathroom floors, etc., should be rendered fungus free if a recurrence of the eruption is to be avoided. This can be accomplished by fumigation for four hours with a formaldehyde candle.

5. Intolerance to the medication. Most of the drugs used in the treatment of fungus infections are of necessity rather strong chemicals. One would therefore naturally expect to encounter an occasional individual whose skin would be irritated by such an application.

Five patients who exhibited an intolerance to Whitfield's ointment form the basis of this report. This represents an extremely low incidence of intolerance in view of the large number of patients who have been treated by this remedy without showing any evidence of irritation. In our practice, Whitfield's ointment has been a routine method of treatment of epidermophytosis. The formula as we have employed it is as follows:

Salicylic acid	2
Benzoic acid	4
Benzoinated lard	30

The usual response to this remedy in our experience has been highly gratifying. Occasional patients have been encountered in whom other remedies were required, and in a few instances the strength of the above formula has been increased two to four times without producing the

slightest evidence of irritation. The above formula, which may be regarded as full strength Whitfield's ointment, is usually prescribed only in those cases in which a diagnosis of fungus infection has been confirmed by positive microscopic findings. Some cases which are strongly suspicious clinically but negative microscopically, are given half strength Whitfield's ointment to apply cautiously. While Whitfield's ointment is apparently innocuous to the average skin, it is important that a suspected case be confirmed microscopically, since such an application would undoubtedly irritate a nonparasitic eczema.

All five of the patients comprising this report presented lesions of the feet which were typical of ringworm infections. In four of the patients the diagnosis was confirmed both by finding the organisms in direct potassium hydroxide preparations of scales and by culture on Sabourraud's medium. *Epidermophyton inguinale* was found twice, *Epidermophyton interdigitale* once, and *Monilia albicans* once. No fungi were found on three examinations in the fifth case, and *Staphlococcus aureus* was the only organism obtained by culture on Sabourraud's medium. The diagnosis of epidermophytosis is therefore open to question in this case, although the eruption presented a fairly typical clinical picture.

An intolerance to the drug was suspected in these cases, not because of any violent reactions, such as one would have reason to expect in a case of dermatitis venenata, but rather because of a lack of response on the part of the lesions, with the subsequent development of what appeared to be new lesions of the disease. Usually there was a temporary improvement for the first few days, probably due to the fungicidal effects of the ointment. Then the lesions would remain more or less stationary for several weeks with the development of new vesicles which in many respects resembled the original infection, but were probably due to the irritating effects of the ointment. Withdrawal of the medication for a week or more would usually be followed by clinical improvement, which in turn was often succeeded by an exacerbation due to the development of more fungi.

Thus, the picture is extremely complicated—improvement due to the fungicidal properties of the medication, followed by exacerbation because of chemical irritation, followed in turn by improvement on withdrawal of the ointment, again followed by exacerbation due to incomplete destruction of fungi, and all the while the lesions maintaining the characteristics of the original fungus infection.

The diagnosis of intolerance to the drug was finally established in each case by a patch test, which was allowed to remain on the flexor surface of the forearm for twenty-four hours. A strongly positive reaction, consisting of redness, vesiculation and crusting, was obtained in each case, within twenty-four hours and lasting several days; in two cases it had not entirely disappeared after three weeks. Of four control subjects tested, only one showed a reaction.

In two cases, after the strongly positive reaction to full strength Whitfield's ointment was obtained, the ingredients were tested separately, with the following results:

		Case 1	Case 2
Salicylic Acid Petrolatum	2 30	negative	very weakly positive
Benzoic Acid Petrolatum	4 30	negative	weakly positive
Benzoinated lard		weakly positive	negative

The following two abbreviated case histories illustrate the clinical course of this complication.

CASE 1.—O. P. H. G., male, aged about forty-two years, had been having intermittent eruptions on his toes and feet for about eleven years. The

Fig. 1.—Positive patch test to Whitfield's ointment in Case 1.

present attack was of about a month's duration, and during this time he had developed for the first time an eruption on the palms and fingers consisting of erythemato-squamous macules. The lesions on the feet were mostly between the toes and consisted of redness, vesiculation and scaling. The patient played tennis a great deal, and had noticed that the eruptions on his feet always flared up after playing tennis. No fungi were found in scrapings from either the feet or the hands. Owing to the negative findings, and yet because of the clinical appearance, the patient was given a half-strength Whitfield's ointment. After four days the feet did not seem sufficiently improved to justify continuing the Whitfield's ointment, especially in view of a second negative microscopic examination, and a crude coal tar ointment was substituted. This was followed by temporary improvement, but in about nine days the feet looked definitely worse, and new vesicles, some of them seropurulent, had appeared. At this time a third microscopic examination was negative, and a culture was taken on

Sabourraud's medium, which after ten days developed a pure culture of *Epidermophyton inguinale*. Half strength Whitfield's ointment was resumed, and after four days the feet were distinctly improved. Six days later, however, the following note was made: "Better, but slight extension of vesiculation on feet, suggesting either an intolerance to Whitfield's ointment or a 'phytid' reaction." The hands which had been regarded originally as a "phytid" reaction had by this time nearly cleared up under bland applications.

Whitfield's ointment was again discontinued and the patient was instructed to apply bismuth violet 0.4 per cent to the feet once daily after opening all vesicles. Five days later the feet seemed better, but the hands had flared up again, suggesting a renewed "phytid" reaction to an infection still present on the feet. Full strength Whitfield's ointment was then prescribed for the feet. The feet improved rapidly for about four days; then the condition became stationary and within a few days more new vesicles had appeared on the sole. Mosaic forms very suggestive of degenerated mycelia were isolated from some of these lesions.

At this time, a patch test with full strength Whitfield's ointment was applied to the forearm, resulting after twenty-four hours in a strongly positive eczematoid reaction, which was still visible after three weeks. As stated above, the individual ingredients tested separately gave practically no reactions. The irritating effects were therefore due to some chemical reaction taking place after the ingredients were combined.

As soon as it was determined that the Whitfield's ointment was probably a factor in causing the eruption to persist, it was permanently discontinued, and the lesions improved slowly under fractional doses of x-ray, mild tar ointments, 1 per cent salicylate acid, etc., although there were temporary exacerbations after the use of 1 per cent thymol and half strength tincture of iodine. At the last visit the condition of the feet looked very good except for slight scaling in several interdigital spaces and a small area of redness and scaling on each of two fingers.

CASE 2.—W. L. S., male, has had an eruption on the left foot for two years. For the past three weeks he has used a proprietary ointment consisting of a modified Whitfield's ointment with thymol. The eruption consisted of redness, vesicles and scaling, involving the anterior part of the sole, the side of the big toe and the last two interdigital spaces. Microscopic examinations of scrapings on this and three subsequent visits were negative, but, about ten weeks after the initial visit, mycelia and spores were found which looked like monilia. This was confirmed by a culture on Sabourraud's medium.

Under Whitfield's ointment with several rest periods of a week, the eruption fluctuated, at times improving, again appearing considerably irritated. After three months of such treatment, during which several other remedies were alternated with the Whitfield's ointment, the foot

was still causing trouble. At this time a patch test of Whitfield's ointment was applied to the arm for twenty-four hours. A strongly positive reaction was obtained which lasted more than a week. Benzoic and salicylic acids tested separately gave very weak reactions, and the benzoinated lard was negative. An ointment containing sulphur, salicylic acid and petrolatum was then used, and three weeks later the eruption was very much improved.

CONCLUSION

Four cases of epidermophytosis of the feet are cited in which the eruption failed to respond to Whitfield's ointment after adequate treatment.

Strongly positive reactions to patch test of Whitfield's ointment were obtained in each case.

In two of these cases in which the ingredients of Whitfield's ointment were tested separately, the reactions were either negative or very weakly positive.

In view of the above findings, it is felt that intolerance to medication must be seriously considered in any case of proved dermatophytosis which fails to respond to adequate treatment.

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FOOD SENSITIZATION DERMATOSES*

ESPECIAL CONSIDERATION OF THE PRIMARY TYPE OF ACNEFORM DISTRIBUTION. PRELIMINARY REPORT

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SENSITIZATION dermatoses of an eczematoid type of the extremities secondary to superficial fungous infections was the subject of a paper[1] read before the American Medical Association a year ago. Many more cases of the type have been studied and treated. Further investigations have led me to believe that there is a primary or dry type of cutaneous manifestations due to food sensitization. It is the aim of this preliminary report to describe briefly this type of eruption. While some thirty cases have been observed and studied, one typical case will be narrated in some detail.

CASE REPORT

A woman of thirty-eight years had had a recurring papular eruption on the cheeks for seventeen years. She had been treated by a number of dermatologists in several cities, according to her history, with temporary success—the eruption reappearing often during a course of x-ray treatments. When first observed she still had the eruption in severe form and was beginning to show mild atrophy and a few telangiectases on the treated areas. She had been informed by her last dermatologic consultant to have no more x-ray treatments. A series of ultraviolet ray treatments had been given with no therapeutic results.

The eruption had the typical acneform distribution on the face. Many erythematous papules were present on each cheek. However, there were no comedones, no so-called "seborrheic dermatitis" of the scalp, and certainly the patient did not have what is usually termed a seborrheic type of skin.

The sudden recurrences suggested that a food sensitization might be the cause of such an eruption. Although cutaneous tests have been of limited value in this type of food sensitization, in this particular case they were of a marked aid in that egg and wheat were positive. Absolute elimination of these and of peaches (found later by using a basic nonallergic diet) has prevented any recurrences. The patient's face has assumed a more normal appearance than it had since the eruption started. (Fig. 1.)

TYPE OF ERUPTION

The eruption is predominantly papular, occasionally becoming pustular. Usually, severe cases leave scars. Practically all cases are con-

*Read before the staff of the West Suburban Hospital at a clinical conference, July 15, 1932.

sidered as acne vulgaris and are treated as such. The chief distribution from acne vulgaris has been cited; the distribution roughly is that of ordinary acne. All cases have been in young adults and middle-aged people in excellent general health. They are considered primary, for no preceding dermatologic syndrome nor any infectious process has been elicited. In the true sense the term "primary" is used only in a relative way, for there must have been metabolic or visceral changes of

Fig. 1.

some type to render the subject allergic to certain foods. Past history of family allergy has been of minor importance.

Theoretically, an allergic person can become sensitive to any food. In practice, the most common ones are considered to be milk, egg, and wheat. In this series, milk was the most common and chocolate next. It is interesting to note in Rowe's monograph[2] what he stated when reporting a woman afflicted with canker sores. ". . . . nearly constant canker sores had been present for years. Elimination diets relieved her of all her symptoms, including a severe long standing acne on her face."

Rowe's contribution of practical elimination diets[2] was of distinct aid where it was not feasible to use skin tests and in many cases where they were used with negative results.

Hopkins and Kesten's[3] slightly changed Rowe diets were also used. Also, I use a basic nonallergic diet consisting of coffee, tea, carrots, lettuce, prunes, plums, apricots, lamb, veal, Rye Krisps, olive oil, plum jam, and peppermint candy. It is used for a week. Then, if there are no new lesions, one can begin to add one food a day, adding at first the least allergic ones. If the offending food is added, new lesions will often appear in four to eight hours. Obviously that food is then eliminated or desensitization may be attempted. Desensitization however has not been tried, as most patients are willing to discontinue the food that causes trouble. Propepton is being used and the results will later be reported together with a more comprehensive consideration of both primary and secondary food sensitization dermatoses. Abstinence of the causative food naturally helps greatly in a large number. Where there is a secondary bacterial infection, local treatment is indicated, such as a weak sulphur ointment. X-ray treatment is of little or no value.

SUMMARY

1. Primary food sensitization eruptions of acneform distribution do occur; differentiation from true acne vulgaris is usually not difficult.

2. Elimination diets of Rowe or of Hopkins and Kesten are of decided diagnostic value. A basic nonallergic diet can also be used. Cutaneous tests may be of help in detecting the offending foods.

3. Treatment of acneform eruptions of the face demand more than x-ray treatments.

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104 South Michigan Ave.

Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

TENTH ANNUAL MEETING, NEW ORLEANS, LA., MAY 8 AND 9, 1932.

(CONTINUED)

The Importance of Molds as Allergic Excitants in Some Cases of Vasomotor Rhinitis. H. S. BERNTON AND CHARLES THOM, WASHINGTON, D. C. (For original article, see page 114.)

DISCUSSION

DR. HARRY L. HUBER, CHICAGO.—I have seen and grown some of these molds and would like to know where I can send them for identification and classification.

DR. ERNEST L. MACQUIDDY, OMAHA, NEB.—I should like to ask whether or not Dr. Bernton has tested the sputum or the nasal secretions for their own molds.

DR. ALBERT H. W. CAULFEILD, TORONTO.—This is more or less complementary to Dr. Rackemann's question. Did he use the same extract for testing and what was the method, by testing or treatment?

DR. RAY M. BALYEAT, OKLAHOMA CITY.—Beginning June 16 last summer we began to run mold curves. Plates were placed, one at eave height and the other on a 110-foot experimental oil derrick at the University of Oklahoma, and we found that on the plates on the 110-foot height there were practically the same number of molds as those on eave level.

We obtained cultures and tested a series of 80 patients with six or eight of the most common molds found on our cultures, and but few were positive with either scratch or intradermal method. The mold curve ran 40 to 300 times as high as all the pollens put together, so apparently patients do not become sensitive to molds and rust that are in the air in our territory. So much has been said concerning molds as an etiologic factor in asthma and hay fever in Holland and some of the other foreign countries. We have found all told in our studies two patients who are clinically sensitive to mold and experimentally sensitive.

DR. HARRY S. BERNTON, WASHINGTON.—The material for testing is secured from the pellicle which is formed on the surface of the liquid media. It is removed, dried, and placed in a desiccator over sulphuric acid. It may also be dried in the electric oven. It is finely pulverized; the powdered mold material is applied to scratches on the skin which have been previously moistened with sodium hydrate.

My method of extracting this material is identical with that of pollen extraction. The extracting solution consists of 66⅔ per cent of glycerine and 33⅓ per cent of Coca's solution. One gram of material is extracted

with 100 c.c. of the glycerinated fluid. Dilutions of 1:1000 and 1:10000 are prepared. The initial dose usually consists of 0.05 c.c. of 1:10000 dilution, administered subcutaneously. For purpose of control 0.2 c.c. or 0.3 c.c. of the extractive fluid alone are injected in the other arm.

Sometimes the subcutaneous tissues of patients are slightly irritated by the glycerine. Accordingly, the use of the extractive fluid itself in larger volume furnishes fairly good evidence of tissue sensitiveness.

DR. VAUGHAN.—Do you mean subcutaneously—no, intracutaneously?

DR. BERNTON.—The intracutaneous application with undiluted glycerine extract should never be performed. It is too irritating. However, intracutaneous tests may be performed with the mold extract, if diluted ten times with salt solution. A control test should always be performed.

DR. HARRY L. HUBER.—How about the identification?

DR. BERNTON.—Well, that is a question. Dr. Thom, who is an authority in the field of mycology, has difficulty in the proper identification of some of the organisms. Even mycologists have controversies. We allergists, therefore, stand on the side lines and look on.

In this connection, I wish to speak of an interesting experience. I came across a patient with a typical history of asthmatic bronchitis, who was found sensitive to the *Aspergillus hortai*. This mold was isolated in Morocco, sent to the Pasteur Institute, and thence forwarded to Washington. Dr. Thom, after studying the mold, felt that it was identical with the *Aspergillus terreus*, which he had described as a common inhabitant of the soil. Dr. Thom furnished me with material made from different strains of the *Aspergillus terreus*. My patient reacted positively to this material. Thus far I have had no other patients who have reacted either to *Aspergillus hortai* or to any strains of the *Aspergillus terreus*.

The skin reactions of my patient throw some light upon the relationship of the molds in question. When it comes to classification and identification of molds, I leave that to the mycologists.

Department of Reviews and Abstracts

Selected Abstracts

Tobacco Sensitiveness in Thromboangiitis Obliterans. Harkavy, J., Hebald, S., and Siebert, S.: Proc. Soc. Exper. Biol. & Med. **30**: 104, 1932.

It had been noted that patients suffering from thromboangiitis were almost universally excessive smokers. However, many equally extensive users of tobacco never developed the disease. The question arose why tobacco should affect one group of individuals and not others. The problem was investigated from the point of view of a possible specific hypersensitiveness to tobacco. The report gives the results in sixty-eight cases of thromboangiitis, the patients varying between the ages of twenty-four and fifty-six years. One hundred and twenty-two controls were used, all males addicted to the use of tobacco and comparable in age, race, duration and amount of tobacco used, with the thromboangiitis patients. Extracts of tobacco were made according to the methods outlined by Coca. Intracutaneous injections of 0.10 c.c. of 1:10 solution were given, and the reactions read within fifteen to twenty minutes. Eighty-three per cent of the thromboangiitis patients gave positive skin reactions. In thirteen out of twenty cases passive transfer of the sensitivity could be demonstrated. In many cases, a multiple sensitization was found, offending reagents being other inhalants or foods. Of the controls, only 10 per cent reacted to tobacco, those reactions being at most only two plus.

Further investigations on this subject are being undertaken.

A New Method of Autoserum Therapy in Severe Cases of Asthma. Jacquelin, A., Turiaf, J., Davous and Reveillaud: Bull. et mem. Soc. med. d. Hôp. de Paris **48**: 557, 1932.

In a series of cases of eczema, the authors had notable success with the autoserum therapy used by Achard and Flandin and later modified by Flandin, i. e., daily small injections of serum given intradermally. By contrast, notably inconsistent results were obtained with this technic in cases of asthma. The question arose whether this contrast in therapeutic success in reactions of the same general order but different focus might not be in the route of introduction of the autogenous serum. Experiments were then undertaken with the intramucous route. Only those patients were used with whom other methods of therapy had failed and whose symptoms were severe and of long duration. Of

thirteen such asthmatic patients, ten were much improved; three remained unaffected. A typical case report is given:

A patient, thirty-one years old, had suffered from asthma for fourteen years. The crises at first rare, increased in frequency and severity until there were several attacks daily and the patient experienced great difficulty in sleeping at night. Many methods of treatment had been tried with little success. No specific sensitization could be discovered. There was a high blood eosinophilia. Autogenous serum was given intramucously in daily doses of 0.2 c.c. to 0.4 c.c. There was no improvement on the first injection; none on the second; on the third, a slight increase in the asthma; on the fourth, intense dyspnea; on the fifth, sudden and complete disappearance of the asthmatic crises. A total of 20 injections were given. There was no recurrence of asthma, and there was, moreover, a considerable improvement in the general condition of the patient.

The authors believe that this modification of the method of Achard and Flandin is worth further experimentation on a larger scale.

The technic is discussed in some detail. There are two methods: the endobuccal route and the nasal route. The nasal route is the more logical and according to the results obtained by the authors, the more positive. But it is also the more delicate for the operator and more painful for the patient. A needle about 4 cm. long is used and the point of injection should be the inferior turbinate or the external face of the immediate neighboring nasal fossae, or the middle turbinate. An important point for the success of the treatment is to make the injection accurately into the thickness of the mucosa. A bleb of intramucous edema should appear at the site of injection. The process is sufficiently painful to warrant the application of a tampon saturated with a solution of 4:100 novocaine. The doses for injection are first 0.2 c.c., then 0.3 c.c., then 0.4 c.c., then 0.5 c.c. This cannot well be increased in the nasal route.

Using the endobuccal route, the dosage may be pushed as high as 1.0 c.c. For this route the needle commonly used in intradermal injections is indicated, and the site of injection should be in the mucosa of the internal face of the cheek about 2 cm. behind the labial commissure. No anesthetic is necessary. Either route may be used, or both. Fresh, unheated serum should be used. Daily injections should be given, to a total of twenty.

The indications for use are particularly in cases of a periodic coryza and asthma of no known specific sensitization. With these, excellent results have been obtained. The suggestion is made that a local desensitization takes place acting directly on the sensitized mucosa or on a neighboring mucosa.

In discussion, Dr. Vallery-Radot cited the severe reactions sometimes known to follow the direct application of a protein to the nasal mucosa, as an indication against the proposed method.

In reply, Dr. Jacquelin stated that in his experience of the proposed method he had never observed severe reactions, and that he saw no apparent reason why a nasal autoserum therapy should provoke any reaction comparable to one that might be elicited by the introduction of allergens into the mucosa.

New Peptone Treatment in Asthma and Other Allergies. Auld, A. G.: Lancet **223**: 67, 1932.

A new peptone treatment is advocated, i. e., Witte's new peptone used in a 5 per cent solution, intramuscularly, together with a 5 per cent solution of propeptan, preferable wheat propeptan.

The author considers that a good many failures in peptone treatment may be due to (1) wrong dosage, (2) failure to give a second or a third course, (3) the nonproduction of a mild pyrogenic reaction. Care is taken to differentiate between this reaction and so-called "protein shock." The mild pyrogenic reaction may be obtained with serum peptone or a small dose of typhoid vaccine intravenously, after which the peptone treatment may often be continued with great success.

The making of serum peptone has been described in a previous communication. The author recently has been using the serum of patients (convalescent serum) who after a long course of peptone treatment have recovered apparently good health. For the treatment of severe cases, this serum first used plain and then mixed with peptone is reported to give good results. A case report is given in which a patient is injected intravenously (5 c.c. to 10 c.c.) for three weeks with convalescent serum. The serum was then incubated with the new peptone ("Peptone Special 30" manufactured by Witte in collaboration with a German University and devoid of the toxic effects of his ordinary peptone) and injected intramuscularly for several weeks, together with wheat peptone. The patient was practically cured of a prolonged and severe asthma. Satisfactory results have been obtained in other cases.

The author also advocates the use of peptone in cases of hay fever and migraine.

Discussion on Specific and Nonspecific Desensitization in Allergic Diseases. Proc. Royal Soc. Med. **25**: 1449, 1932.

G. H. Oriel.—Asthma is not to be considered as synonymous with allergy. Asthma is a symptom, and a certain proportion of the cases can be shown to depend upon allergy. Treatment may be specific or nonspecific. Specific desensitization can be successful only with one protein at a time; nonspecific desensitization seems to affect all sensitization. For nonspecific therapy, various substances have been used: peptone, tuberculin, injections of sulphur, typhoid-paratyphoid vaccine, etc. The results, while undoubtedly beneficial in many cases, are rarely permanent.

Restriction between allergic asthma and other forms of asthma can

be made by: (1) Skin tests to different proteins. (2) Intradermal injections of extracts of human dandruff. Positive skin tests are obtained with this in patients whose asthma depends upon inhaled antigens. Method used by Storm van Leeuwen. (3) Skin tests with a substance, called for convenience "P substance," isolated from the urine of patients with the type of asthma which shows an increase in the amino acids in the blood during attacks. Investigations showed that the "P substance" from a patient with multiple sensitizations gives positive skin tests with asthmatic patients who have been demonstrated to have similar sensitizations, and not with other asthmatic patients who do not. It was further shown that the "P substance" from an asthmatic with multiple sensitizations will give positive skin tests in cases which respond to human dander. Desensitization with "P substance" resulted in one case in a cessation of symptoms.

W. Storm van Leeuwen.—The basis of nonspecific treatment lies in the fact that during the course of acute infectious diseases asthma and other allergic symptoms usually disappear temporarily. The instance of the beneficial effect in this way of lobar pneumonia is cited. Repeated attacks of fever have often been shown to be beneficial. Such patients, however, as are sensitive to certain allergens and cannot avoid subsequent contact with these allergens derive no benefit of any duration from fever treatment. Tuberculin therapy will have a beneficial effect upon all asthmatics who give a positive von Pirquet reaction, treatment, however, being largely dependent for lasting results upon two factors: (1) the quantity of allergens acting upon the patient at home and in his habitual surroundings; (2) climate and atmospheric conditions.

Tuberculin cannot harm the patient, and the percentage is high of those cases which may profit by the treatment. In nonspecific therapy, the substance used should be preferably of a nonprotein nature unable to produce anaphylactic symtoms. A 0.5 per cent solution of precipitated sulphur in oil is suggested for use, as being simple and cheap. The only drawback is pain, which starts some hours after the injection and may persist for several hours. The sulphur treatment seldom fails to give at least temporary relief.

Dr. George Bray suggested that the active principle of the Storm van Leeuwen dander test for allergic individuals might be histamine. The hydrolysis of dander gives rise to many amines of which histamine is one; physiologic tests with dander and histamine solutions give similar reactions; similar skin tests can be obtained with each; both give a Zimmermann's color reaction for histamine.

Asthma Due to a Local Anesthetic. Waldbott, G. L.: J. A. M. A. **99**: 1492, 1932.

A case is reported in which a patient, relieved for fourteen months from perennial asthma, suffered a severe attack of asthma upon the application of a cocaine crystal to the mucosa of the septum. Epineph-

rine was resorted to to relieve the paroxysm. A similar attack was again induced upon a second attempt to apply cocaine to the nasal septum for the purpose of local anesthesia. A scratch test with 3 per cent cocaine solution produced erythema but no typical wheal.

Another case report is given in which death followed almost immediately upon the application of procaine hydrochloride. It is suggested that some of the unexplained cases of sudden death during a local anesthetic may be attributed to anaphylaxis.

A Rapid and More Accurate Method of Determining the Pollen Content of the Air. Duke, W. W.: J. A. M. A. **99**: 1686, 1932.

A machine is described for a quicker and more accurate analysis of the pollen content of air than the twenty-four-hour gravity method generally in use. The instrument blows air at the constant rate of about forty miles an hour against a greasy slide placed in the holder. It is estimated that the number of pollen grains deposited on 1.8 square centimeters of surface, multiplied by two or three, approximates crudely the content of a cubic yard of air.

By the use of this machine, the source of error in the gravity method, i. e., the variation in the velocity of air currents, is eliminated. An estimate sufficiently accurate for clinical use can be made within a few minutes. The author points out the fact, however, that such readings do not represent the twenty-four-hour mean obtained by the gravity method.

The Local and Constitutional Pathology of Bronchial Asthma. Macdonald, I. G.: Ann. Int. Med. **6**: 253, 1932.

Collected from 3,690 autopsies at the Hospital of the University of Michigan since 1896, eight cases are reported, in five of which death can be laid to asphyxia or cardiac failure during or immediately following a paroxysm of bronchial asthma. In the other three cases, while the criteria of bronchial asthma were established, death occurred from intercurrent infection. The ages of the patients ranged from thirteen years to seventy-five years. Particular attention, in the study of this series, is paid to the pathology of the individual structural layers and units of the bronchi and peribronchial tissue. The case reports are given in considerable detail. Individual findings vary, but common to most of the cases are found: (a) thickening and hyaline change of the basement membrane of the bronchi, (b) eosinophilia, (c) varying degrees of hypertrophy of the bronchial musculature, (d) bronchial sacculations occurring through the mouths of the mucous glands, (e) epithelial changes such as hypertrophy and metaplasia.

Commenting upon the claim made by Alexander, Luten, and Kountz, that in long-continued bronchial asthma, the heart remains remarkably free from damage, attention is called to the almost constant ventricular

hypertrophy as evidenced in this series by the measurements of the heart wall.

The author takes exception to the admission of "bacterial" bronchial asthma as an entity. In his opinion, clinical, immunologic, and pathologic evidence fails to support the concept. He identifies the allergic state with an altered reaction of an inheritable, hypoplastic type of constitution. Each of the cases in the series is shown by tables to be of a thymicolymphatic constitution. Tables are also given showing the bronchial pathology and the presumable etiology and cardiac condition.

Contact Dermatitis (Venenata). Balyeat, R. M., Rinkel, H. J., and Stemen, T. R.: Am. J. M. Sc. **184**: 547, 1932.

The Nelenium plant, in one form or another, is found to grow abundantly throughout the United States. One or more species is reported in every state in the Union, while profusion and wide distribution occur in about 50 per cent of the states. The plant grows commonly along the roadside, around barns, and in wheat fields, and is used not infrequently as a border plant in gardens. Hence, the possibility of human contact with the plant is great. The authors report several cases of severe dermatitis due to the Neleniums. The irritant was found to be secreted upon the surfaces of the leaves and flowers in the form of a resin, soluble in absolute alcohol, benzene and ether, and relatively insoluble in water. A 10 per cent solution of the resinous material in olive oil was used for patch tests. In addition to a marked local reaction, severe systemic reactions were sometimes encountered, manifested by abdominal cramps with diarrhea. Tests should, therefore, be made with great care.

Cutaneous Reactions in States of Hypersensitiveness. Sezary, A., and Maurie, G.: Bull. et. Mem. Soc. méd. d. hôp. de Paris **48**: 105, 1932.

Attention is drawn to the variability in results in skin tests. Some of the factors determining this variability are briefly discussed. Three definite types of reaction are noted: (1) Patients suffering from rheumatism or urticaria, Quincke's edema, eczema, and some asthmatics in whom there is a positive cutaneous reaction. This reaction is obtained by scarifying the skin with a vaccino-style loaded with antigen. An urticarial papule appears within ten to twenty minutes from the moment of contact. The reaction disappears within a few hours or even within a few minutes. Constitutional reaction of some severity may frequently be provoked in this group of patients. Intradermal tests in this group give similar results with an even greater tendency toward constitutional reactions. Positive results are also to be obtained in this group with the Prausnitz-Küstner technic.

(2) Patients suffering from tuberculosis, gonorrhea, the malady of

Nicolas and Favre, and various other conditions, in whom the cutaneous reaction does not always give results. In this group the intradermal reaction is the most reliable. This reaction is characterized by a skin papule which, more delayed than the cutaneous reaction, appears from twenty-four to forty-eight hours after inoculation and persists for some days. The epidermal and the Prausnitz-Küstner technic give predominantly negative results.

(3) Patients suffering from certain allergic eczemas and skin disorders of various types in whom the cutaneous reaction is negative and the intradermal reaction is of a different kind from that observed in type 2. In type 3 the intradermal reaction appears generally within twenty-four to forty-eight hours after inoculation but often does not reach its maximum for several days and may persist for several weeks. In this type also, there is a positive epidermic reaction. This is obtained by applying directly to the skin a compress soaked with antigen which is left in place for several hours. The Prausnitz-Küstner reaction in many cases is negative.

Mixed types are recognized; also those which are clinically hypersensitive but in whom no positive skin test can be obtained. In this latter class fall:

(A) Subjects belonging to type 2 in whom the cutaneous reactions disappear during the course of infection.

(B) Subjects belonging to type 2 in whom the cutaneous reactions disappear during the course of treatment for infection.

(C) Subjects belonging to type 3 in whom the intradermal reaction is negative during the weeks which follow the clinical manifestations.

(D) Subjects belonging to type 1 who had positive cutaneous reactions during infancy and who remained hypersensitive, but whose skin reactivity disappeared with age. In this category come many adults with negative skin reactions, whose intolerance is of an alimentary origin.

(E) Subjects clinically positive who give negative skin tests, whose hypersensitiveness is localized not in the skin but in the nervous system.

In summary, it is suggested that type 1 may consist of those individuals in whom there is a general hypersensitiveness of the organism (antibodies circulating in the blood stream and the interstitial fluid) and in whom the hypersensitiveness is strongly marked.

Type 2 may consist of individuals in whom the intolerance can be attributed to an antibody not circulating free in the blood stream but fixed probably in the dermal tissue, more especially in the conjunctive or reticuloendothelial tissue.

Type 3 may consist of individuals in whom the intolerance is purely epidermal.

In mixed types the hypersensitiveness is complex. In those cases where no positive reaction can be elicited many hypotheses must be considered.